



Hypothesized neuroprotective effect of minocycline against COVID-19-induced stroke and neurological dysfunction: possible role of matrix metalloprotease signaling pathway

Ali Aghajani Shahrivar¹ · Zahra Khakpourian¹ · Fatemeh Majidi² · Sarvenaz Sobhani¹ · Natalie Coleman-Fuller³ · Mina Gholami⁴ · Majid Motaghinejad¹

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Abstract

Severe Acute Respiratory Syndrome Coronavirus-2 (COVID-19) is a respiratory disease that causes dysfunction in respiration. Since late 2019, this virus has infected and killed millions of people around the world and imposed many medical and therapeutic problems in the form of a pandemic. According to recent data, COVID-19 disease can increase the risk of stroke, which can be deadly or cause many neurological disorders after the disease. During the last two years, many efforts have been made to introduce new therapies for management of COVID-19-related complications, including stroke. To achieve this goal, several conventional drugs have been investigated for their possible therapeutic roles. Minocycline, a broad-spectrum, long-acting antibiotic with anti-inflammatory and antioxidant properties, is one such conventional drug that should be considered for treating COVID-19-related stroke, as indirect evidence indicates that it exerts neuroprotective effects, can modulate stroke occurrence, and can play an effective and strategic role in management of the molecular signals caused by stroke and its destructive consequences. The matrix metalloprotease (MMP) signaling pathway is one of the main signaling pathways involved in the occurrence and exacerbation of stroke; however, its role in COVID-19-induced stroke and the possible role of minocycline in the management of this signaling pathway in patients with COVID-19 is unclear and requires further investigation. Based on this concept, we hypothesize that minocycline might act via MMP signaling as a neuroprotective agent against COVID-19-induced neurological dysfunction, particularly stroke.

Keywords Minocycline · COVID-19 · Stroke · Neurodegeneration · MMP signaling pathway

Abbreviations

MMP matrix metalloprotease
COVID-19 Severe Acute Respiratory Syndrome (SARS) Coronavirus (CoV)-2
ECM extracellular matrix
TIMPs tissue inhibitors to metalloproteinases

EC endothelial cells
AP-1 activator protein-1
NF-κB nuclear factor kappa B
TNF-α tumor necrosis factor-alpha
IL-β Interleukin-1 beta
CREB cAMP responses element binding protein
BDNF brain derived neurotrophic factor
Akt protein kinase B
JAK/STAT Janus kinase-signal transducer and activator of transcription
COX cyclooxygenase
NOS nitric oxide synthase

✉ Majid Motaghinejad
m.motaghinejad@sbmu.ac.ir; dr.motaghinejad6@gmail.com

¹ Chronic Respiratory Disease Research Center (CRDRC), National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

² Department of Pharmaceutical Biomaterials, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

³ Department of Veterinary and Biomedical Sciences, University of Minnesota, Saint Paul, MN 55108, USA

⁴ College of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Introduction

First identified in 2019 as Severe Acute Respiratory Syndrome (SARS) Coronavirus (CoV)-2 (COVID-19), COVID-19 infection has since caused a worldwide pandemic with

serious medical implications. The World Health Organization reports that, as of May 2022, COVID-19 has infected more than 522 million people, causing more than 6.27 million deaths worldwide (Moolla et al. 2021; Pomara et al. 2021; Böttcher et al. 2021). Although SARS-CoV-1 and Middle East Respiratory Syndrome Coronavirus are similar to COVID-19 and cause comparable symptoms, these viruses did not cause pandemics due to their lower severity and infectivity (Begum et al. 2021; da Salva et al. 2021; Gholami et al. 2021; Molaei et al. 2021). Coronaviruses may directly or indirectly cause vasculopathy, coagulopathy, and stroke. Subsequently, these types of stroke can lead to neural degeneration, mainly caused by hypoxia/ischemia (Becker 2020; Gholami et al. 2021; Roberts et al. 2020). Despite abundant data regarding COVID-19-induced stroke, the main signaling pathway in this lethal phenomenon is unknown and its molecular basis remains undefined (Frisullo et al. 2020; Kahraman and Vural 2022; Nannoni et al. 2021; Sánchez and Rosenberg 2022; Al-Gburi et al. 2021). Therefore, it is important to evaluate COVID-19-induced stroke and subsequent neurodegeneration and characterize the underlying molecular mechanisms to determine new treatment strategies against COVID-19. The matrix metalloprotease (MMP) pathway is one of the main signaling pathways involved in stroke and hypoxia/ischemia phenomenon (Costru-Tasnic et al. 2021; Montaner et al. 2019); however, its exact role in pathogenesis of COVID-19-induced stroke remains unclear (Frisullo et al. 2020; Kahraman and Vural 2022; Nannoni et al. 2021; Sánchez and Rosenberg 2022; Al-Gburi et al. 2021).

Introduction of new drugs and advancement of potential therapies for patients with COVID-19 should be aimed at preventing COVID-19 post-infection complications such as stroke and neurodegeneration (Gholami et al. 2021; Laudanski et al. 2021; Menéndez et al. 2022). One drug that might have neuroprotective effects and anti-stroke properties is minocycline (Laudanski et al. 2021; Liu et al. 2021). Previous studies indicate that minocycline has a protective effect on stroke-induced destructive signaling pathways; however, its effect on COVID-19-induced stroke and hypoxia/ischemia and its involvement in MMP is unknown and needs assessment (Liu et al. 2021; Lu et al. 2021). We hypothesize that minocycline might provide protective effects against COVID-19-induced stroke via inhibition of the MMP signaling pathway, which has a critical role in stroke and ischemia/hypoxia.

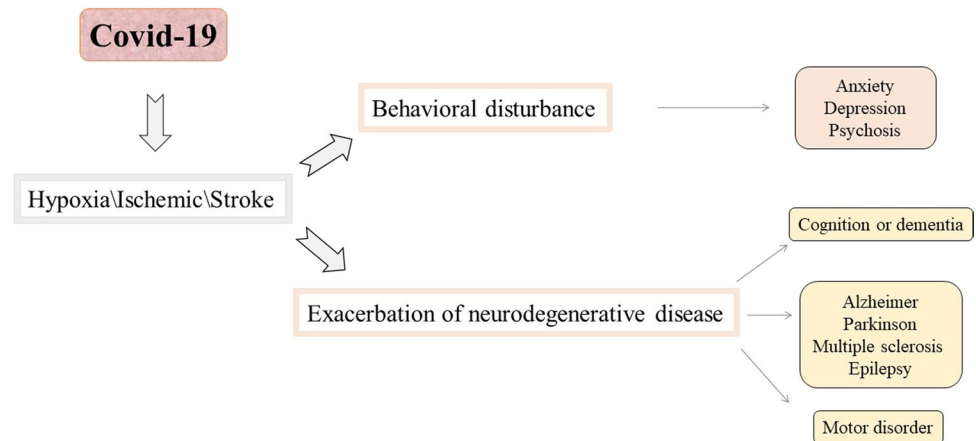
COVID-19-induced stroke

Coronaviruses may directly or indirectly cause vascular degeneration, coagulation cascade disturbances and stroke; subsequently, these types of stroke can lead to neural degeneration (Becker 2020; Roberts et al. 2020). Patients infected

with SARS-CoV-2 show development of abnormal blood clotting as an inflammatory response to the virus (Lazzaroni et al. 2021; Roberts et al. 2020), thereby causing increased risk of blood clots, which can lead to stroke if a blood clot blocks an artery to the brain (Hess et al. 2020; Lazzaroni et al. 2021; Markus and Brainin 2020). Recent analyses show that 1.4% of COVID-19 cases had acute cardiovascular disease, with 87.4% of these occurring as acute ischemic stroke. Moreover, compared to uninfected individuals with stroke, patients with COVID-19-associated stroke were younger, had higher NIH stroke scale values (NIHSS), higher frequency of large vessel occlusion and higher in-hospital mortality rate (Nannoni et al. 2021; Zhang et al. 2021). Stroke is more likely to occur in patients with severe COVID-19 infections who have pre-existing vascular risk factors (Tang and Zheng 2022; Wijeratne et al. 2020). Although more epidemiologic population-based studies are required to further assess the incidence of stroke in individuals with COVID-19, several studies have suggested a close relationship between COVID-19 and stroke (Nannoni et al. 2021; Tang and Zheng 2022; Zhang et al. 2021). As stroke can cause neurological dysfunction, it is likely that COVID-19-induced neurobehavioral and neurological dysfunction such as cognition impairment, dementia, epilepsy, motor disorder, anxiety, and mood-related disorders are caused by cellular disorders and neurodegeneration associated with stroke (Feyissa et al. 2019; Gillespie et al. 2011; Kooi et al. 2017) (Fig. 1).

Indirect evidence indicates that COVID-19-induced stroke involves mitochondrial dysfunction, oxidative stress, inflammation, and apoptosis in neuronal cells (Avula et al. 2020; Spence et al. 2020). Additionally, mitochondrial dysfunction in stroke-affected tissues can damage multiple parts of the brain and central nervous system (Spence et al. 2020; Wang et al. 2020). Stroke can cause disturbances in oxidative stress balances (Avula et al. 2020; Rodrigo et al. 2013; Spence et al. 2020), activation of lipid and protein peroxidation in neuronal cells, reduction of antioxidant activity and inhibition of brain capacity via free radical scavenging (Cherubini et al. 2005; Orellana-Urzúa et al. 2020; Rodrigo et al. 2013). Based on this concept, it is likely that COVID-19-induced stroke causes neurodegeneration via activation of oxidative stress pathways (Cherubini et al. 2005; Orellana-Urzúa et al. 2020; Rodrigo et al. 2013). Stroke-induced neuro-inflammation, apoptosis and neuronal cell death have been well studied, and stroke-associated neurodegenerative events likely involve these events (Anrather and Iadecola 2016; Nilupul et al. 2006). Similarly, stroke associated with COVID-19 infection likely causes activation of neuro-inflammation, apoptosis and neuronal cell cascades, resulting in neurodegeneration (McAlpine et al. 2021; Wijeratne et al. 2020). COVID-19-induced stroke-possibly via activation of mitochondrial dysfunction, oxidative stress, inflammation, and

Fig. 1 COVID-19-induced stroke and hypoxia can cause behavioral disturbances such as anxiety, depression and psychosis, and can exacerbate neurodegenerative disorders and diseases such as cognition impairment, dementia, epilepsy, motor disorders, multiple sclerosis, Parkinson’s disease and Alzheimer’s disease



apoptosis-likely affects neuronal cells, causing COVID-19-induced neurological and neurobehavioral dysfunction.

Despite the preponderance of indirect data from a range of studies, the signaling pathway for COVID-19-induced stroke is unknown. Understanding the involved signaling cascades is critical to preventing and treating COVID-19-induced stroke.

The MMP signaling pathway definition and its role in stroke

Degradation of extracellular matrix (ECM) components is important for promoting normal embryonic development, angiogenesis and cell repair in the body. MMPs are a group of extracellular zinc-dependent proteolytic enzymes that play critical roles in ECM degradation (Rosell and Lo 2008; Yang and Rosenberg 2015). However, MMP signaling malfunction can cause abnormal ECM degradation, which can lead to vascular complications. This large family of MMP enzymes contains small proteins such as MMP-7 and large enzymes such as MMP-14. Although these enzymes differ in substrate specificity, they are arranged similarly in structure, with each containing a catalytic zinc site, a hemopexin site, a transmembrane site and a fibronectin binding site (Rosell and Lo 2008; Yang and Rosenberg 2015). Functionally, these enzymes are first secreted in a latent form that protects cells from damage, and then activated to degrade ECM and recruit inflammatory cells to the damaged area. The MMPs are immediately inactivated by proteins such as tissue inhibitors to metalloproteinases (TIMPs), thereby maintaining normal homeostasis in the ECM (Chirco et al. 2006; Rosell and Lo 2008).

This family of protein/enzymes contain constitutive enzymes, such as MMP-2 and MMP-14, and inducible enzymes such as MMP-3 and MMP-9 (Ramos-Fernandez et al. 2011; Yang and Rosenberg 2015). The constitutive enzymes play a critical role in maintaining the integrity of

basement membranes and acting to prevent the overgrowth of ECM (Rosell and Lo 2008; Yang and Rosenberg 2015), whereas inducible enzymes are commonly activated after initiation of neuro-inflammation and free radical cascades ECM (Rosell and Lo 2008; Yang and Rosenberg 2015). MMP-2, also known as gelatinase A, and MMP-9 play critical roles in astrocytic foot processes for binding to endothelial cells (EC) (Jin et al. 2010; Zhao et al. 2006). MMP-2 is activated by a proteolytic process that is mediated by a complex of MMP-2, TIMP2, and MMP-14; formation of this complex causes activation of MMP-14, which activates MMP-2. This interplay between activation and inactivation prevents extensive damage caused by MMP-2, while allowing removal of excess ECM to maintain the integrity of the basal lamina around blood vessels (Jin et al. 2010; Zhao et al. 2006). Microglia, macrophages, and infiltrating neutrophils are the primary sources of MMP-3 and MMP-9, which are activated after neuro-inflammation via the oxidative stress pathway. MMP-8 and MMP-13 are also involved in injury cascades in periodontal tissue, however, their role in stroke is unclear (Adibhatla and Hatcher 2008). Neuro-inflammatory cascade components, such as activator protein-1 (AP-1) and nuclear factor kappa B (NF-κB), play critical roles in activation of MMP-3 and MMP-9. Cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β) also cause activation of MMP-3 and MMP-9 (Rosell and Lo 2008; Yang and Rosenberg 2015). During neuro-inflammation caused by viral or bacterial infection, for example, a number of cytokines are released, which activate MMP-3 and MMP-9 (Lakhan et al. 2013; Rosell and Lo 2008; Yang and Rosenberg 2015) (Fig. 2).

As depicted in Fig. 2, the MMP pathway is one of the main signaling pathways involved in stroke and hypoxia/ischemia (Costru-Tasnic et al. 2021; Montaner et al. 2019). Hypoxia/ischemia events activate two pathways. In the first pathway, activation of the hypoxia-inducing factor causes activation of MMP-2 (Kim and Han 2006; Loor and Schumacker 2008). In the second pathway, activation of

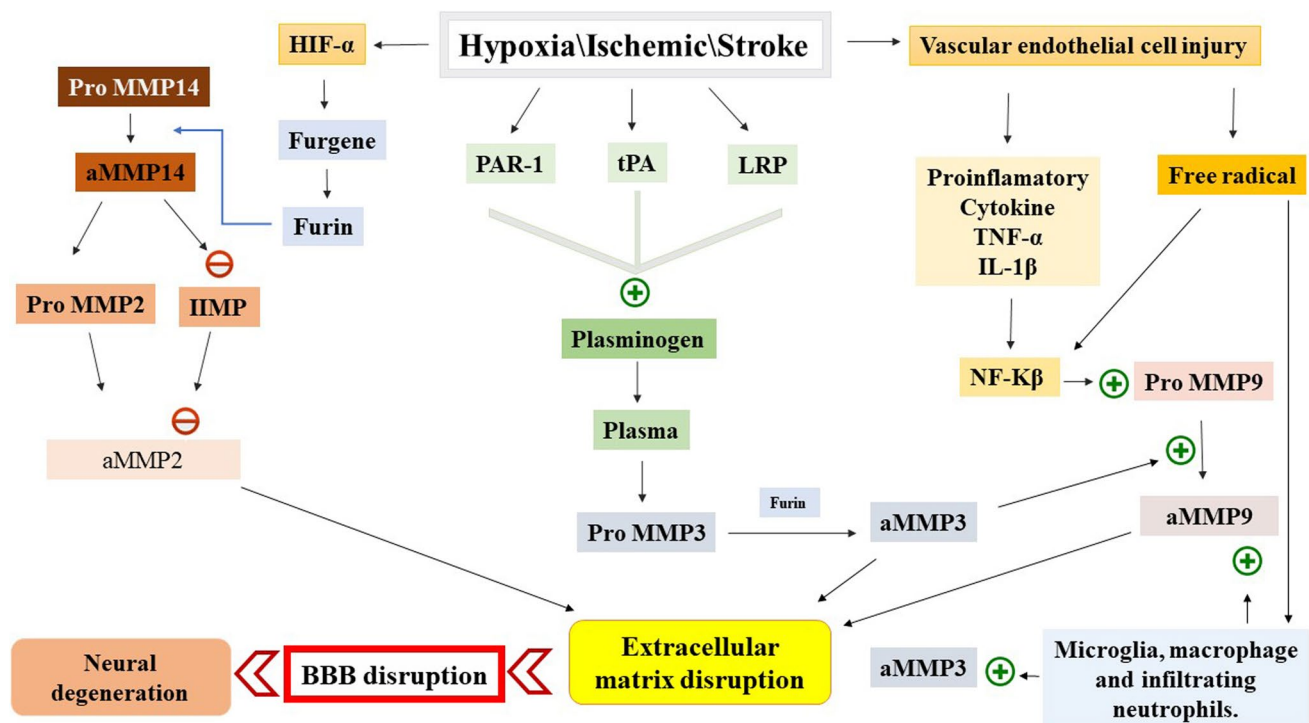


Fig. 2 Hypoxia/ischemia/stroke can cause vascular endothelia injury which can lead to production of pro-inflammatory cytokines, such as TNF- α and IL-1 β , and free radicals. This phenomenon causes activation of NF- κ B, which leads to activation of MMP-9. In a second pathway, hypoxia/ischemia/stroke can cause activation of PAR-1, t-PA and LRP, activating the conversion of plasminogen to plasmin, which in turn activates furin, leading to MMP3 activation. In a third pathway, hypoxia/ischemia/stroke activates furin via activation of HIF- α , and furin triggers the activation of MMP14; active MMP14 causes activation of MMP2, and TIMP regulates MMP2 activity. In addition to these pathways that activate MMP-2, MMP-3 and MMP-

9, other components such as microglia, macrophage and infiltrating neutrophils activate MMP-9, all of which lead to disruption of the extracellular matrix. Disruption of the extracellular matrix can lead to BBB disruption, which initiates neural degeneration. Abbreviations: TNF- α , tumor necrosis factor-alpha; IL-1 β , interleukin-1 beta; NF- κ B, nuclear factor kappa B; PAR, protease activated receptor 1; t-PA, tissue plasminogen activator; LRP, lipoprotein receptor-related protein; MMP, matrix metalloproteinase; HIF, hypoxia-inducible factor; TIMP, tissue inhibitors of matrix metalloproteinase; BBB, blood brain barrier

cytokines, such as TNF- α and IL-1 β , lead to activation of MMP-3 and MMP-9 (Du et al. 2020; Loor and Schumacker 2008). Subsequently, MMP-2 and -9 levels are elevated several hours after ischemia (Ramos-Fernandez et al. 2011). Activation of MMP-2 and -9 cause degradation of ECM, which leads to disruption of the ECM of the blood brain barrier (BBB) (Rempe et al. 2016; Webb et al. 2017); this phenomenon can cause increased susceptibility of the brain to intrinsic and extrinsic toxic agents, leading to post-stroke neurodegeneration (Rempe et al. 2016).

While the role of MMP signaling is a prominent feature in the molecular biology of stroke and in post-stroke neurodegeneration, its involvement in COVID-19-associated stroke and its potential role in the pathophysiology of coronavirus-induced neurological dysfunction and post-stroke neurodegeneration have not been clarified. On the other hand, stroke is associated with numerous neurodegenerative events and diseases such as cognition impairment, dementia, epilepsy, motor disorder, anxiety, and mood

related disorder (Fig. 1). Thus, as the MMP signal pathway is involved in coronary stroke, we hypothesize that MMP signaling may play a similar critical role in the occurrence of neurological complications associated with COVID-19-associated stroke. Therefore, it is important to evaluate the role of the MMP signaling pathway in COVID-induced stroke and post-stroke-induced neurological dysfunction.

Minocycline may function via the MMP signaling pathway to prevent COVID-19-induced stroke

New drugs and the advancement of potential therapies for patients with COVID-19 should be aimed at preventing COVID-19-induced downstream effects such as stroke and neurodegeneration (Gholami et al. 2021; Laudanski et al. 2021; Menéndez et al. 2022). An important aspect of proposing drugs for the prevention and management of COVID-19-induced stroke and neurodegeneration should consider their neuroprotective role (Gholami et al. 2021;

Laudanski et al. 2021; Menéndez et al. 2022). Furthermore, the proposed drugs should target the underlying mechanisms of COVID-19-induced stroke and post-stroke neurological events (Gholami et al. 2021a, b; Laudanski et al. 2021; Menéndez et al. 2022). To this end, candidate agents should target the MMP signaling pathway and have both anti-stroke and neuroprotective effects.

Due to its neuroprotective effects, minocycline is a candidate drug as a potential treatment for COVID-19-induced stroke (Oliveira et al. 2020; Sing et al. 2020; Xiao 2020). Minocycline is a broad-spectrum and long-acting antibiotic with anti-inflammatory and antioxidant properties (Wang et al. 2017; Zheng et al. 2019). Despite being an antibiotic, in recent years, different effects and properties of this drug have been elucidated, particularly concerning its positive effects on brain disorders and neurodegenerative disease (Hiskens et al. 2021; Motaghinejad and Motevalian 2022; Strickland et al. 2021; Yamasaki et al. 2021). Minocycline is a potent neuroprotective agent, showing protective effects against several neurodegenerative diseases and disorders such as Alzheimer Disease, Parkinson’s Disease, multiple sclerosis, cerebral ischemia, and drug (alcohol and nicotine) abuse-induced neurodegeneration (Berens et al. 2020; Gholami and Motaghinejad 2021; Motaghinejad et al. 2020; Romero-Miguel et al. 2021; Sharma et al. 2010; Thomas and Le 2004). Our earlier studies showed that minocycline has antioxidant, anti-inflammatory, and anti-apoptotic effects (Abbaszadeh et al. 2018; Naderi et al. 2017; Yang et al. 2020). Minocycline has been evaluated for its effectiveness in stroke (Chen et al. 2017; Li et al. 2022; Lu et al. 2021), and these studies indicated that minocycline can inhibit ischemia/hypoxia-induced neural cell damage and injury (Chen et al. 2017; Li et al. 2022; Lu et al. 2021). Furthermore, the use of minocycline for treating multiple types of stroke has been evaluated in both animal and human studies (Fagan et al. 2010, 2011). Several previous studies suggest that the mechanism by which minocycline exerts its effects against stroke and ischemia events involves MMPs (Chang et al. 2017; Switzer et al. 2011).

Previous studies showed that minocycline causes neural function repair and modulates oxidative stress (Naderi et al. 2020; Sakata et al. 2012; Matsukawa et al. 2009). Additionally, minocycline inhibits activation of lipid and protein peroxidation in neuronal cells during neurodegenerative events such as stroke, causes activation of antioxidant activity, and activates brain capacity via free radical scavenging (Kraus et al. 2005; Plane et al. 2010). Experimental and clinical studies have showed that minocycline exerts anti-inflammation properties by reducing oxidative stress, decreasing apoptosis, inhibiting leukocyte migration and microglial activation, and decreasing MMP activity (Chen et al. 2017). Furthermore, minocycline positively affects neural stem cell survival by

reducing cytokine production and inhibiting pro-apoptosis and apoptotic biomarkers (Chen et al. 2017; Lampl et al. 2007; Rueger et al. 2012; Vedantam and Moller 2015). Minocycline exerts its protective effects against lethal stroke by modulating activation of mitochondrial biogenesis and preventing mitochondrial dysfunction (Chen et al. 2017; Zhang 2019). In addition to its effects against stroke-induced mitochondrial dysfunction, oxidative stress, inflammation, and apoptosis, minocycline protects neuronal cells against experimental stroke or ischemia via inhibition of MMP-2 and MMP-9, two major components of the MMP- signaling pathway (Machado et al. 2006; Switzer et al. 2011). Moreover, minocycline prevents increased BBB permeability, edema, and hemorrhage after ischemic stroke by inhibiting MMP-2 and 9 (Chang et al. 2017; Switzer et al. 2011).

Other studies indicate that minocycline acts via activation of protective proteins, such as cAMP responses element binding protein (CREB), brain derived neurotrophic factor (BDNF) and protein kinase B (Akt), to modulate stroke-induced neuronal damage (Motaghinejad et al. 2020; Zhao et al. 2015). Similar previous studies demonstrated that minocycline confers neuroprotective effects against stroke-induced neurological dysfunction via inhibition of inflammatory cascades such as the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, NF-κB, cyclooxygenase (COX) and nitric oxide synthetize (NOS)

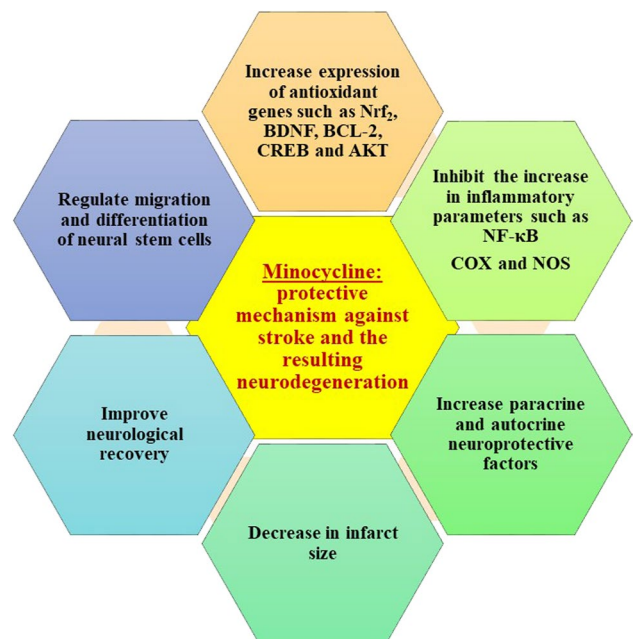


Fig. 3 Proposed mechanism of minocycline in the management of stroke and ischemia events. Abbreviations: Nfr2, nuclear factor erythroid 2-related factor 2; BDNF, brain derived neurotrophic factor; BCL-2, B-cell lymphoma 2; CREB, cAMP responses element binding protein; AKT, protein kinase B; NF-κB, nuclear factor kappa B; COX, cyclooxygenase; NOS, nitric oxide synthase

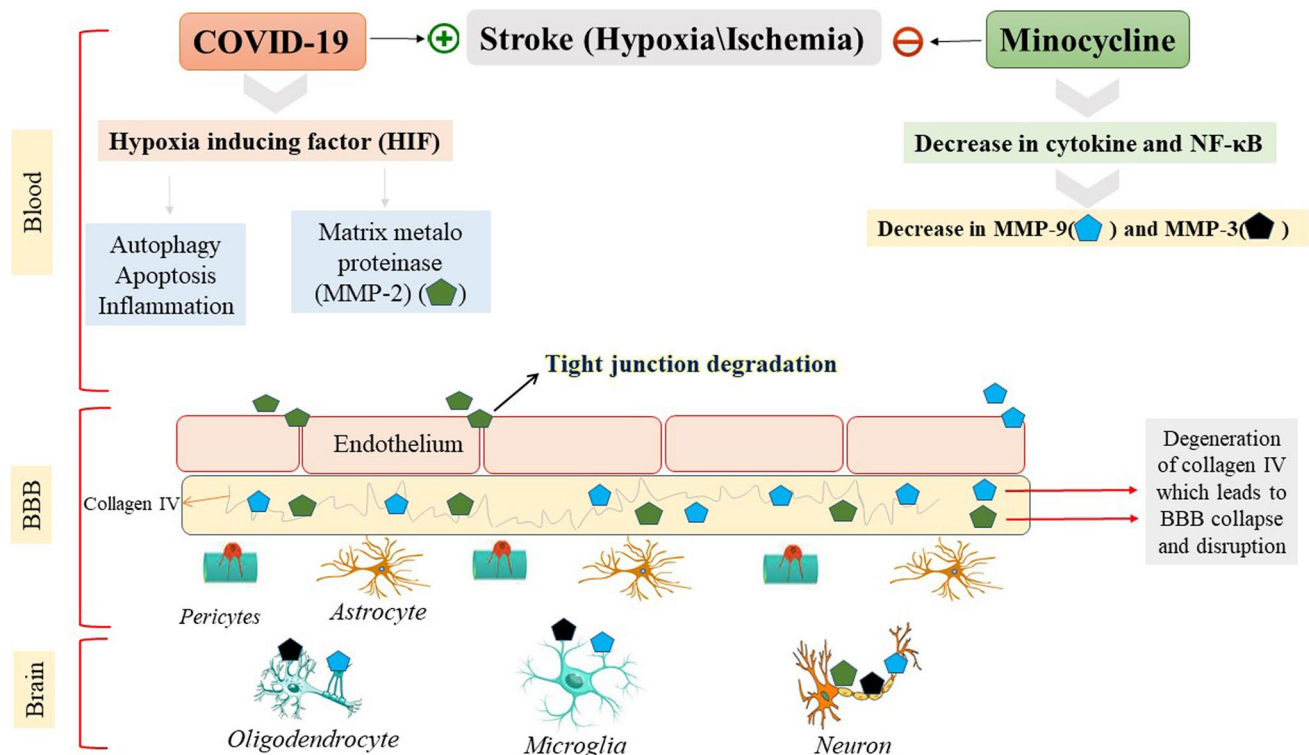


Fig. 4 Possible mechanism of minocycline: modulation of MMP pathway during stroke. Minocycline may provide protective effects against COVID-19-induced stroke, neurodegeneration, and organ damage. COVID-19-induced hypoxia/ischemia likely causes activation of HIF, which causes activation of MMP-2. This coronavirus-induced hypoxia/ischemia can cause activation of cytokines such

as $\text{TNF-}\alpha$ and $\text{NF-}\kappa\text{B}$, which leads to activation of MMP-9. Both MMP-2 and -9 cause degradation of the ECM, which leads to BBB disruption and degeneration of critical organ tissue. Minocycline is a good candidate for treating COVID-19-induced stroke due to its inhibitory effect on the MMP signaling pathway, neurodegeneration, and organ damage. Abbreviations: ECM, extracellular matrix

(Chen et al. 2017; Liu et al. 2021; Yi et al. 2019). Further, neurotrophic signaling and migration of neural stem cells were modulated by administration of minocycline in stroke-induced neuronal dysfunction (Kim and Suh 2009). Other work has suggested that minocycline can reduce infarct size during stroke, likely by modulating apoptosis and inflammation (Fig. 3).

Despite multiple studies showing the positive effect of minocycline against stroke and other neurological dysfunction, its effects in COVID-19-induced stroke and post-stroke-induced neurodegeneration and neurological disorders remain unclear. While several reports have suggested that minocycline might have therapeutic effects for improving COVID-19 symptoms, its effects on COVID-19-induced stroke, as well as its effect on intracellular signals, are unknown (Oliviera et al. 2020; Singh et al. 2020; Xiao 2020). Several studies have revealed a positive effect of minocycline in modulating MMPs in stroke (Machado et al. 2006); however, it remains unknown whether minocycline is effective against COVID-19-induced stroke, neurodegeneration and neurological

dysfunctional and whether it exerts its effects via modulation of the MMP signaling pathway. Figure 4 depicts a schematic of how minocycline may provide protective effects against COVID-19-induced stroke, neurodegeneration, and organ damage.

Conclusions

COVID-19-induced stroke and neurologic dysfunction has emerged as a new disease process that could afflict millions worldwide for the duration of the pandemic. With the aim of developing drug therapies to treat patients with COVID-induced stroke, we hypothesize that minocycline might be effective against COVID-19-induced stroke and neurological dysfunction by modulating the MMP pathway. Thus, we believe minocycline should be evaluated in animal models and human subjects for its protective effects against COVID-19-induced stroke and neurodegeneration, with an emphasis on the evaluation of the MMP signaling cascade.

Declarations

Competing interest The authors have no competing interests to declare that are relevant to the content of this article.

References

- Abbaszadeh A, Darabi S, Hasanvand A, Amini-Khoei H, Abbasnezhad A, Choghakhori R et al (2018) Minocycline through attenuation of oxidative stress and inflammatory response reduces the neuropathic pain in a rat model of chronic constriction injury. *Iran J Basic Med Sci* 21:138–144. <https://doi.org/10.22038/IJBMS.2017.24248.6053>
- Adibhatla RM, Hatcher JF (2008) Tissue plasminogen activator (tPA) and matrix metalloproteinases in the pathogenesis of stroke: therapeutic strategies. *CNS Neurol Disord Drug Targets* 7:243–253. <https://doi.org/10.2174/187152708784936608>
- Al-Gburi S, Beissert S, Günther C (2021) Molecular mechanisms of vasculopathy and coagulopathy in COVID-19. *Biol Chem* 402:1505–1518. <https://doi.org/10.1515/hsz-2021-0245>
- Anrather J, Iadecola C (2016) Inflammation and stroke: An overview. *Neurotherapeutics* 13:661–670. <https://doi.org/10.1007/s13311-016-0483-x>
- Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S et al (2020) COVID-19 presenting as stroke. *Brain Behav Immun* 87:115–119. <https://doi.org/10.1016/j.bbi.2020.04.077>
- Becker RC (2020) COVID-19-associated vasculitis and vasculopathy. *J Thromb Thrombolysis* 50:499–511. <https://doi.org/10.1007/s11239-020-02230-4>
- Begum J, Mir NA, Dev K, Buyamayum B, Wani MY, Raza M (2021) Challenges and prospects of COVID-19 vaccine development based on the progress made in SARS and MERS vaccine development. *Transbound Emerg Dis* 68:1111–1124. <https://doi.org/10.1111/tbed.13804>
- Berens SC, Bird CM, Harrison NA (2020) Minocycline differentially modulates human spatial memory systems. *Neuropsychopharmacology* 45:2162–2169. <https://doi.org/10.1038/s41386-020-00811-8>
- Böttcher L, D’Orsogna MR, Chou T (2021) Using excess deaths and testing statistics to determine COVID-19 mortalities. *Eur J Epidemiol* 36:545–558. <https://doi.org/10.1007/s10654-021-00748-2>
- Chang JJ, Kim-Tenser M, Emanuel BA, Jones GM, Chapple K, Alikhani A et al (2017) Minocycline and matrix metalloproteinase inhibition in acute intracerebral hemorrhage: a pilot study. *Eur J Neurol* 24:1384–1391. <https://doi.org/10.1111/ene.13403>
- Chen Y, Cai Z, Ke Z (2017) Antineuroinflammation of minocycline in stroke. *Neurologist* 22:120–126. <https://doi.org/10.1097/nrl.0000000000000136>
- Cherubini A, Ruggiero C, Polidori MC, Mecocci P (2005) Potential markers of oxidative stress in stroke. *Free Radic Biol Med* 39:841–852. <https://doi.org/10.1016/j.freeradbiomed.2005.06.025>
- Chirco R, Liu X-W, Jung K-K, Kim H-RC (2006) Novel functions of TIMPs in cell signaling. *Cancer Metastasis Rev* 25:99–113. <https://doi.org/10.1007/s10555-006-7893-x>
- Costru-Tasnici E, Gavriluc M, Manole E (2021) The importance of matrix metalloproteinases in the prognosis of acute ischemic stroke patients. *Moldovan Med J*. <https://doi.org/10.52418/moldovan-med-j.64-3.21.09>
- da Silva PG, Mesquita JR, de São José Nascimento M, Ferreira VAM (2021) Viral, host and environmental factors that favor anthropozoonotic spillover of coronaviruses: An opinionated review, focusing on SARS-CoV, MERS-CoV and SARS-CoV-2. *Sci Total Environ* 750:141483. <https://doi.org/10.1016/j.scitotenv.2020.141483>
- Du X, Yang J, Liu C, Wang S, Zhang C, Zhao H et al (2020) Hypoxia-inducible factor 1 α and 2 α have beneficial effects in remote ischemic preconditioning against stroke by modulating inflammatory responses in aged rats. *Front Aging Neurosci* 12:54. <https://doi.org/10.3389/fnagi.2020.00054>
- Fagan SC, Cronin LE, Hess DC (2011) Minocycline development for acute ischemic stroke. *Transl Stroke Res* 2:202–208. <https://doi.org/10.1007/s12975-011-0072-6>
- Fagan SC, Waller JL, Nichols FT, Edwards DJ, Pettigrew LC, Clark WM et al (2010) Minocycline to improve neurological outcome in stroke (MINOS): a dose-finding study. *Stroke* 41:2283–2287. <https://doi.org/10.1161/STROKEAHA.110.582601>
- Feyissa AM, Hasan TF, Meschia JF (2019) Stroke-related epilepsy. *Eur J Neurol* 26:18–e3. <https://doi.org/10.1111/ene.13813>
- Frisullo G, Bellavia S, Scala I, Piano C, Morosetti R, Brunetti V et al (2020) Stroke and COVID19: Not only a large-vessel disease. *J Stroke Cerebrovasc Dis* 29:105074. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105074>
- Gholami M, Nozarnezhad R, Motaghinejad M (2021a) Hypothetical protective effects of crocin carotenoid against Coronavirus-induced organ damage: The possible role of the NF- κ B signaling pathway. *Iran J Med Sci* 46:228–229. <https://doi.org/10.30476/ijms.2021.88513.1921>
- Gholami M, Safari S, Ulloa L, Motaghinejad M (2021b) Neuropathies and neurological dysfunction induced by coronaviruses. *J Neurovirol* 27:380–396. <https://doi.org/10.1007/s13365-021-00977-x>
- Gillespie DC, Joice S, Lawrence M, Whittick J (2011) Interventions for post-stroke disturbances of mood and emotional behaviour: recommendations from SIGN 118. *Int J Ther Rehabil* 18:166–174. <https://doi.org/10.12968/ijtr.2011.18.3.166>
- Hess DC, Eldahshan W, Rutkowski E (2020) COVID-19-related stroke. *Transl Stroke Res* 11:322–325. <https://doi.org/10.1007/s12975-020-00818-9>
- Hiskens MI, Vella RK, Schneiders AG, Fenning AS (2021) Minocycline improves cognition and molecular measures of inflammation and neurodegeneration following repetitive mTBI. *Brain Inj* 35:831–841. <https://doi.org/10.1080/02699052.2021.1909139>
- Jin R, Yang G, Li G (2010) Molecular insights and therapeutic targets for blood-brain barrier disruption in ischemic stroke: critical role of matrix metalloproteinases and tissue-type plasminogen activator. *Neurobiol Dis* 38:376–385. <https://doi.org/10.1016/j.nbd.2010.03.008>
- Kahraman A, Vural A (2022) Increased incidence of acute ischemic stroke in COVID-19 patients. *Acibadem Univ Saglik Bilim Derg* 13. <https://doi.org/10.31067/acusaglik.997072>
- Kim H-S, Suh Y-H (2009) Minocycline and neurodegenerative diseases. *Behav Brain Res* 196:168–179. <https://doi.org/10.1016/j.bbr.2008.09.04>
- Kim HY, Han S-H (2006) Matrix metalloproteinases in cerebral ischemia. *J Clin Neurol* 2:163–170. <https://doi.org/10.3988/jcn.2006.2.3.163>
- Kooi Ong L, Rohan Walker F (2017) Is stroke a neurodegenerative condition? A critical review of secondary neurodegeneration and amyloid-beta accumulation after stroke. *AIMS Med Sci* 4:1–16. <https://doi.org/10.3934/medsci.2017.1.1>
- Kraus RL, Pasieczny R, Lariosa-Willingham K, Turner MS, Jiang A, Trauger JW (2005) Antioxidant properties of minocycline: neuroprotection in an oxidative stress assay and direct radical-scavenging activity. *J Neurochem* 94:819–827. <https://doi.org/10.1111/j.1471-4159.2005.03219.x>
- Lakhan SE, Kirchgessner A, Tepper D, Leonard A (2013) Matrix metalloproteinases and blood-brain barrier disruption in acute ischemic stroke. *Front Neurol* 4. <https://doi.org/10.3389/fneur.2013.00032>

- Lampl Y, Boaz M, Gilad R, Lorberboym M, Dabby R, Rapoport A et al (2007) Minocycline treatment in acute stroke: an open-label, evaluator-blinded study. *Neurology* 69:1404–1410. <https://doi.org/10.1212/01.wnl.0000277487.04281.db>
- Laudanski K, Hajj J, Restrepo M, Siddiq K, Okeke T, Rader DJ (2021) Dynamic changes in central and peripheral neuro-injury vs. Neuroprotective serum markers in COVID-19 are modulated by different types of anti-viral treatments but do not affect the incidence of late and early strokes. *Biomedicines* 9:1791. <https://doi.org/10.3390/biomedicines9121791>
- Lazzaroni MG, Piantoni S, Masneri S, Garrafa E, Martini G, Tincani A et al (2021) Coagulation dysfunction in COVID-19: The interplay between inflammation, viral infection and the coagulation system. *Blood Rev* 46:100745. <https://doi.org/10.1016/j.blre.2020.100745>
- Li L, Xing X, Li Q, Zhang Q, Fu L, Liu Y (2022) Minocycline improves learning and memory functions in ischemic stroke rats via reduction of cerebral ischemia-induced neuroinflammation and apoptosis. *Trop J Pharm Res* 20:287–292. <https://doi.org/10.4314/tjpr.v20i2.10>
- Liu Y, Li Z, Khan S, Zhang R, Wei R, Zhang Y et al (2021) Neuroprotection of minocycline by inhibition of extracellular matrix metalloproteinase inducer expression following intracerebral hemorrhage in mice. *Neurosci Lett* 764:136297. <https://doi.org/10.1016/j.neulet.2021.136297>
- Loor G, Schumacker PT (2008) Role of hypoxia-inducible factor in cell survival during myocardial ischemia-reperfusion. *Cell Death Differ* 15:686–690. <https://doi.org/10.1038/cdd.2008.13>
- Lu Y, Zhou M, Li Y, Li Y, Hua Y, Fan Y (2021) Minocycline promotes functional recovery in ischemic stroke by modulating microglia polarization through STAT1/STAT6 pathways. *Biochem Pharmacol* 186:114464. <https://doi.org/10.1016/j.bcp.2021.114464>
- Machado LS, Kozak A, Ergul A, Hess DC, Borlongan CV, Fagan SC (2006) Delayed minocycline inhibits ischemia-activated matrix metalloproteinases 2 and 9 after experimental stroke. *BMC Neurosci* 7:56. <https://doi.org/10.1186/1471-2202-7-56>
- Markus HS, Brainin M (2020) COVID-19 and stroke-A global World Stroke Organization perspective. *Int J Stroke* 15:361–364. <https://doi.org/10.1177/1747493020923472>
- Matsukawa N, Yasuhara T, Hara K, Xu L, Maki M, Yu G et al (2009) Therapeutic targets and limits of minocycline neuroprotection in experimental ischemic stroke. *BMC Neurosci* 10:126. <https://doi.org/10.1186/1471-2202-10-126>
- McAlpine LS, Zubair AS, Maran I, Chojecka P, Lleva P, Jasne AS et al (2021) Ischemic stroke, inflammation, and endotheliopathy in COVID-19 patients. *Stroke* 52:e233–e238. <https://doi.org/10.1161/STROKEAHA.120.031971>
- Menéndez SG, Martín Giménez VM, Holick MF, Barrantes FJ, Manucha W (2022) COVID-19 and neurological sequelae: Vitamin D as a possible neuroprotective and/or neuroreparative agent. *Life Sci* 297:120464. <https://doi.org/10.1016/j.lfs.2022.120464>
- Molaei S, Dadkhah M, Asghariazar V, Karami C, Safarzadeh E (2021) The immune response and immune evasion characteristics in SARS-CoV, MERS-CoV, and SARS-CoV-2: Vaccine design strategies. *Int Immunopharmacol* 92:107051. <https://doi.org/10.1016/j.intimp.2020.107051>
- Montaner J, Ramiro L, Simats A, Hernández-Guillamon M, Delgado P, Bustamante A et al (2019) Matrix metalloproteinases and ADAMs in stroke. *Cell Mol Life Sci* 76:3117–3140. <https://doi.org/10.1007/s00018-019-03175-5>
- Moolla MS, Lahri S, Parker A, Schrueder N (2021) Going where the data are: Connecting to Trello for daily statistics in the COVID-19 era and beyond. *S Afr Med J* 111:1032–1033. <https://doi.org/10.7196/SAMJ.2021.v111i11.16134>
- Motaghinejad M, Farokhi N, Motevalian M, Safari S (2020) Molecular, histological and behavioral evidences for neuroprotective effects of minocycline against nicotine-induced neurodegeneration and cognition impairment: Possible role of CREB-BDNF signaling pathway. *Behav Brain Res* 386:112597. <https://doi.org/10.1016/j.bbr.2020.112597>
- Motaghinejad M, Motevalian M (2022) Neuroprotective properties of minocycline against methylphenidate-induced neurodegeneration: Possible role of CREB/BDNF and Akt/GSK3 signaling pathways in rat hippocampus. *Neurotox Res* 40:689–713. <https://doi.org/10.1007/s12640-021-00454-7>
- Naderi Y, Panahi Y, Barreto GE, Sahebkar A (2020) Neuroprotective effects of minocycline on focal cerebral ischemia injury: a systematic review. *Neural Regen Res* 15:773–782. <https://doi.org/10.4103/1673-5374.268898>
- Naderi Y, Sabetkasaei M, Parvardeh S, Zanjani TM (2017) Neuroprotective effect of minocycline on cognitive impairments induced by transient cerebral ischemia/reperfusion through its anti-inflammatory and anti-oxidant properties in male rat. *Brain Res Bull* 131:207–213. <https://doi.org/10.1016/j.brainresbull.2017.04.010>
- Nannoni S, de Groot R, Bell S, Markus HS (2021) Stroke in COVID-19: A systematic review and meta-analysis. *Int J Stroke* 16:137–149. <https://doi.org/10.1177/1747493020972922>
- Nilupul Perera M, Ma HK, Arakawa S, Howells DW, Markus R, Rowe CC et al (2006) Inflammation following stroke. *J Clin Neurosci* 13:1–8. <https://doi.org/10.1016/j.jocn.2005.07.005>
- Oliveira AC, Richards EM, Karas MM, Pepine CJ, Raizada MK (2020) Would repurposing minocycline alleviate neurologic manifestations of COVID-19? *Front Neurosci* 14:577780. <https://doi.org/10.3389/fnins.2020.577780>
- Orellana-Urzúa S, Rojas I, Libano L, Rodrigo R (2020) Pathophysiology of ischemic stroke: Role of oxidative stress. *Curr Pharm Des* 26:4246–4260. <https://doi.org/10.2174/1381612826666200708133912>
- Plane JM, Shen Y, Pleasure DE, Deng W (2010) Prospects for minocycline neuroprotection. *Arch Neurol* 67:1442–1448. <https://doi.org/10.1001/archneurol.2010.191>
- Pomara C, Sessa F, Ciaccio M, Dieli F, Esposito M, Giammanco GM et al (2021) COVID-19 vaccine and death: Causality algorithm according to the WHO eligibility diagnosis. *Diagnostics* (Basel) 11:955. <https://doi.org/10.3390/diagnostics11060955>
- Ramos-Fernandez M, Bellolio MF, Stead LG (2011) Matrix metalloproteinase-9 as a marker for acute ischemic stroke: a systematic review. *J Stroke Cerebrovasc Dis* 20:47–54. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2009.10.008>
- Rempe RG, Hartz AMS, Bauer B (2016) Matrix metalloproteinases in the brain and blood-brain barrier: Versatile breakers and makers. *J Cereb Blood Flow Metab* 36:1481–1507. <https://doi.org/10.1177/0271678X16655551>
- Roberts KA, Colley L, Agbaedeng TA, Ellison-Hughes GM, Ross MD (2020) Vascular manifestations of COVID-19 - thromboembolism and microvascular dysfunction. *Front Cardiovasc Med* 7:598400. <https://doi.org/10.3389/fcvm.2020.598400>
- Rodrigo R, Fernández-Gajardo R, Gutiérrez R, Matamala JM, Carrasco R, Miranda-Merchak A et al (2013) Oxidative stress and pathophysiology of ischemic stroke: novel therapeutic opportunities. *CNS Neurol Disord Drug Targets* 12:698–714. <https://doi.org/10.2174/1871527311312050015>
- Romero-Miguel D, Lamanna-Rama N, Casquero-Veiga M, Gómez-Rangel V, Desco M, Soto-Montenegro ML (2021) Minocycline in neurodegenerative and psychiatric diseases: An update. *Eur J Neurol* 28:1056–1081. <https://doi.org/10.1111/ene.14642>
- Rosell A, Lo EH (2008) Multiphasic roles for matrix metalloproteinases after stroke. *Curr Opin Pharmacol* 8:82–89. <https://doi.org/10.1016/j.coph.2007.12.001>
- Rueger MA, Muesken S, Walberer M, Jantzen SU, Schnakenburg K, Backes H et al (2012) Effects of minocycline on endogenous neural stem cells after experimental stroke. *Neuroscience* 215:174–183. <https://doi.org/10.1016/j.neuroscience.2012.04.036>

- Sakata H, Niizuma K, Yoshioka H, Kim GS, Jung JE, Katsu M et al (2012) Minocycline-preconditioned neural stem cells enhance neuroprotection after ischemic stroke in rats. *J Neurosci* 32:3462–3473. <https://doi.org/10.1523/JNEUROSCI.5686-11.2012>
- Sánchez KE, Rosenberg GA (2022) Shared inflammatory pathology of stroke and COVID-19. *Int J Mol Sci* 23:5150. <https://doi.org/10.3390/ijms23095150>
- Sharma VK, Goyal A, Ganti SS (2010) Minocycline, an antibiotic and a neuroprotective: justifying role in Alzheimer's disease. *Asian J Pharmaceut Clin Res* 3(3):142–145
- Singh H, Kakkar AK, Chauhan P (2020) Repurposing minocycline for COVID-19 management: mechanisms, opportunities, and challenges. *Expert Rev Anti Infect Ther* 18:997–1003. <https://doi.org/10.1080/14787210.2020.1782190>
- Spence JD, de Freitas GR, Pettigrew LC, Ay H, Liebeskind DS, Kase CS et al (2020) Mechanisms of stroke in COVID-19. *Cerebrovasc Dis* 49:451–458. <https://doi.org/10.1159/000509581>
- Strickland BA, Bakhsheshian J, Emmanuel B, Amar A, Giannotta SL, Russin JJ et al (2021) Neuroprotective effect of minocycline against acute brain injury in clinical practice: A systematic review. *J Clin Neurosci* 86:50–57. <https://doi.org/10.1016/j.jocn.2021.01.005>
- Switzer JA, Hess DC, Ergul A, Waller JL, Machado LS, Portik-Dobos V et al (2011) Matrix metalloproteinase-9 in an exploratory trial of intravenous minocycline for acute ischemic stroke. *Stroke* 42:2633–2635. <https://doi.org/10.1161/STROKEAHA.111.618215>
- Tang X, Zheng F (2022) A review of ischemic stroke in COVID-19: currently known pathophysiological mechanisms. *Neurol Sci* 43:67–79. <https://doi.org/10.1007/s10072-021-05679-0>
- Thomas M, Le WD (2004) Minocycline: neuroprotective mechanisms in Parkinson's disease. *Curr Pharm Des* 10:679–686. <https://doi.org/10.2174/1381612043453162>
- Vedantam S, Moller AR (2015) Minocycline: a novel stroke therapy. *J Neurol Stroke* 2:1–6. <https://doi.org/10.15406/jnsk.2015.02.00073>
- Wang H, Tang X, Fan H, Luo Y, Song Y, Xu Y et al (2020) Potential mechanisms of hemorrhagic stroke in elderly COVID-19 patients. *Aging* 12:10022–10034. <https://doi.org/10.18632/aging.103335>
- Wang Z, Nong J, Shultz RB, Zhang Z, Kim T, Tom VJ et al (2017) Local delivery of minocycline from metal ion-assisted self-assembled complexes promotes neuroprotection and functional recovery after spinal cord injury. *Biomaterials* 112:62–71. <https://doi.org/10.1016/j.biomaterials.2016.10.002>
- Webb AH, Gao BT, Goldsmith ZK, Irvine AS, Saleh N, Lee RP (2017) Inhibition of MMP-2 and MMP-9 decreases cellular migration, and angiogenesis in in vitro models of retinoblastoma. *BMC Cancer* 17. <https://doi.org/10.1186/s12885-017-3418-y>
- Wijeratne T, Gillard Crewther S, Sales C, Karimi L (2020) COVID-19 pathophysiology predicts that ischemic stroke occurrence is an expectation, not an exception-A systematic review. *Front Neurol* 11:607221. <https://doi.org/10.3389/fneur.2020.607221>
- Xiao B (2020) Minocycline might be an adjunctive therapy option for the treatment of COVID-19: In silico screening, structure-affinity relationship, and literature review. *Res Square*. <https://doi.org/10.21203/rs.3.rs-40141/v1>
- Yang Q, Luo L, Sun T, Yang L, Cheng L-F, Wang Y et al (2020) Chronic minocycline treatment exerts antidepressant effect, inhibits neuroinflammation, and modulates gut microbiota in mice. *Psychopharmacology* 237:3201–3213. <https://doi.org/10.1007/s00213-020-05604-x>
- Yang Y, Rosenberg GA (2015) Matrix metalloproteinases as therapeutic targets for stroke. *Brain Res* 1623:30–38. <https://doi.org/10.1016/j.brainres.2015.04.024>
- Yamasaki T, Hatori A, Zhang Y, Mori W, Kurihara Y, Ogawa M et al (2021) Neuroprotective effects of minocycline and KML29, a potent inhibitor of monoacylglycerol lipase, in an experimental stroke model: a small-animal positron emission tomography study. *Theranostics* 11:9492–9502. <https://doi.org/10.7150/thno.64320>
- Yi Q, Tan F-H, Tan J-A, Chen X-H, Xiao Q, Liu Y-H et al (2019) Minocycline protects against myocardial ischemia/reperfusion injury in rats by upregulating MCP1P1 to inhibit NF-κB activation. *Acta Pharmacol Sin* 40:1019–1028. <https://doi.org/10.1038/s41401-019-0214-z>
- Zhang G (2019) Minocycline impedes mitochondrial-dependent cell death and stabilizes expression of hypoxia inducible factor-1α in spinal cord injury. *Arch Med Sci* 15:475–483. <https://doi.org/10.5114/aoms.2018.73520>
- Zhang S, Zhang J, Wang C, Chen X, Zhao X, Jing H et al (2021) COVID-19 and ischemic stroke: Mechanisms of hypercoagulability (Review). *Int J Mol Med* 47:1. <https://doi.org/10.3892/ijmm.2021.4854>
- Zhao B-Q, Wang S, Kim H-Y, Storrie H, Rosen BR, Mooney DJ et al (2006) Role of matrix metalloproteinases in delayed cortical responses after stroke. *Nat Med* 12:441–445. <https://doi.org/10.1038/nm1387>
- Zhao Y, Xiao M, He W, Cai Z (2015) Minocycline upregulates cyclic AMP response element binding protein and brain-derived neurotrophic factor in the hippocampus of cerebral ischemia rats and improves behavioral deficits. *Neuropsychiatr Dis Treat* 11:507–516. <https://doi.org/10.2147/NDT.S73836>
- Zheng W, Zhu X-M, Zhang Q-E, Cheng G, Cai D-B, He J et al (2019) Adjunctive minocycline for major mental disorders: A systematic review. *J Psychopharmacol* 33:1215–1226. <https://doi.org/10.1177/02698811198582860>

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