Minocycline in brain- a bench to bed side view

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ABSTRACT

Originally developed as an antibiotic Minocycline has shown a variety of aspects that makes Minocycline a versatile molecule with diversified roles. Beside an antibiotic it has proven to be beneficial in different disorders and the potential of Minocycline to attenuate the severity of disease like stroke, cerebral ischemia, multiple sclerosis, spinal-cord injury, Parkinson's disease, epeilepsy, traumatic brain injury, Huntington's disease, and amyotrophic lateral sclerosis and Alzheimer's disease makes it a centre of fascination in research circles. Despite progress in understanding the pathogenesis of several neurological disorders, our knowledge of the mechanisms leading to neuronal cell loss, glial dysfunction, and vascular remodeling is incomplete. In this review, we describe the evidences and various mechanisms which may be responsible for the efficacy of Minocycline in several neurological disorders and introduce the emerging investigation of minocycline in clinical neurology. The encouraging results of minocycline in experimental neurology make it a potential therapeutic target in human neurological diseas

Introduction

Minocycline, an antibiotic of the tetracycline family, has attracted considerable interest for its theoretical therapeutic applications in neurodegenerative diseases1. Minocycline is a semi-synthetic second generation tetracycline that has now been in use for more than 40 years. It was synthesized in 1967 by the erstwhile Lederle Laboratories (part of American Cyanamid that was subsequently bought by American Home Products Corp. in 1994 which in turn became a part of Pfizer Inc. in 2009), and became commercially available from 1972 under the brand name of Minocin, after getting United States Food and Drug Administration (FDA) approval in June 19712.

Minocycline, the most lipid soluble and most active tetracycline antibiotic, is a long-acting tetracycline and indicated in the treatment of Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsial pox and tick fevers caused by Rickettsiae, upper respiratory tract infections caused by Streptococcus pneumoniae and for the treatment of asymptomatic carriers of Neisseria meningitides. Minocycline's effects are related to the inhibition of protein synthesis. Minocycline passes directly through the lipid bilayer or passively diffuses through porin channels in the bacterial membrane. Tetracyclines like minocycline bind to the 30S ribosomal subunit, preventing the binding of tRNA to the mRNA-ribosome complex and interfering with protein synthesis3.

Minocycline is a semi synthetic tetracycline that has been in use for over 30 years to treat pneumonia and acne vulgaris, infections of the skin, genital, and urinary systems4 and molecule capable of crossing the blood–brain barrier and penetrates the CSF of human beings better than doxycycline and other tetracyclines7.

Minocycline has been reported to have neuroprotective effects in various experimental models of cerebral ischemia8, traumatic brain injury, 9 amyotrophic lateral sclerosis (ALS) 10, Parkinson's diseases (PD) 11, kainic acid treatment, 12 Huntington's disease (HD) 13, and multiple sclerosis14. Additionally, minocycline was reported to attenuate white matter damage in a rat model of chronic cerebral hypoperfusion15.

Stress conditions such as ultraviolet, endoplasmic reticulum (ER) stress, and reactive oxygen species (ROS) elicit a cellular adaptive response for the coordinated expression of stress-responding genes. One of these responses is the phosphorylation of eIF2α (Eukaryotic initiation translation factor 2 α) 16. A common strategy in the cellular response to stress signals is to shut down protein synthesis.17 Translation of eukaryotic mRNAs is regulated primarily at the level of initiation18.

Binding of the initiator tRNA, Met-tRNAiMet, to the 40S subunit is facilitated by the eIF2a which forms a ternary complex with GTP and Met-tRNAiMet. Although the phosphorylation of eIF2a can inhibit general translation19, it stimulates the mRNA translation of the transcriptional modulator ATF416 that inhibits CREB (Cyclic AMP responsive element binding protein, helpful in neuronal survival) activity, thereby down regulating its immediate early genes (BDNF, c-fos, EGR-1)18. Prolonged ER stress is linked to the pathogenesis of several neurodegenerative disorders, which include cerebral ischemia, PD, and AD20,21Minocycline exerts neuroprotective actions in vitro and in vivo model of AD by attenuation of phosphorylation of eIF-2a thereby downregulating downstream cascade responsible for neuronal death22.

Neuroinfalammation plays a decisive role in pathogenesis of almost every neurodegenerative disorder and activated microglia and reactive astrocytes, contribute not only to the production of cytokines, chemokines, reactive oxygen species, and neurotoxic substances, but also to neurotrophic factors23.

The relationship between this cell activation and the cognitive dysfunction in Aβ depositing diseases is not well understood, partially because of the complex responses generated by activated inflammatory cells.

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Minocycline treatment has led to reduction of microglia, interleukin and TNFalpha in several models.

Nitric oxide (NO), a multifunctional mediator produced by and acting on various cells, participates in inflammatory and autoimmune-mediated tissue destruction. NO is produced by a family of ubiquitous enzymes, nitric oxide synthases (NOSs).The overexpression of NOS in a variety of inflammatory tissues has led many to conclude that the modulation of NO synthesis and action could represent a new approach to the treatment of inflammatory, neurological and autoimmune conditions. Minocycline exert pleiotropic functions independent of their antimicrobial activity, which include inhibition of NOS expression, NO production, thus inflammation. It has been speculated that the pleiotropic properties of Minocycline may be partially attributed to their ability to target another multifunctional signaling molecule24.

Poly (ADP-ribose) polymerase-1 (PARP-1) participates in DNA repair as DNA damage activates PARP-1 to catalyze extensive polymerization of ADP-ribose from its substrate NAD1 to nuclear proteins, most notably PARP-1 itself 25. It plays a key role in neuronal death and survival under stress conditions. When activated by DNA damage, PARP-1 consumes NAD to form branched poly (ADP-ribose) on target proteins. Poly (ADPribose) formation on histones and enzymes involved in DNA repair appears to facilitate DNA repair by preventing chromatid exchange and by loosening histone wrapping. Poly (ADPribose) formation also has effects on gene transcription through interactions with transcription factors, notably NFkB and PARP-1 inhibition or gene deletion attenuates the brain microglial response to cytokines and other triggers. Extensive PARP-1 activation can, in addition, lead to neuronal death through mechanisms linked to NAD depletion and release of apoptosis inducing factor from the mitochondria. PARP-1 activation is a key mediator of neuronal death during excitotoxicity, ischemia, and oxidative stress.

Furthemore, mitochondria play important roles in cell death through the release of pro-apoptotic factors such as cytochrome c and apoptosis-inducing factor (AIF), which activates caspase-dependent and caspase-independent cell death, respectively. PARP-1 is emerging as an important activator of caspase-independent cell death. PARP-1 generates the majority of long, branched poly (ADP-ribose) (PAR) polymers following DNA damage. Overactivation of PARP-1 initiates a nuclear signal that propagates to mitochondria and triggers the release of AIF. AIF then shuttles from mitochondria to the nucleus and induces peripheral chromatin condensation, large-scale fragmentation of DNA and, ultimately, cytotoxicity26.

The activities of the pro-apoptotic proteins caspase 3 and poly (ADP-ribose) polymerase (PARP) are increased in brain cells during normal ageing27. The occurrence of rapid mitochondrial depolarization by NO in hippocampal neurons. Energy depletion soon follows, and the facile conclusion is that decreased production of ATP is entirely responsible. However, NO also may increase ATP hydrolysis by the cell, particularly by activation of PARP28. Minocycline has a direct inhibitory effect on PARP-1 at submicromolar concentrations and has been found to be neuroprotective.

Metalloproteinases (MMPs) are upregulated in multiple sclerosis, autoimmune encephalomyelitis (EAE) and several neurological disorders and they have several detrimental effects including breakdown of the blood–brain barrier, promotion of neuroinflammation, and neurotoxicity29. Minocycline inhibited the enzymatic activity of MMPs30. Furthermore, the good safety record of minocycline in long-term oral use to treat acne is an important consideration for treatment of a chronic disease such as multiple sclerosis. Thus, it is relevant that minocycline is a direct inhibitor of MMP enzymatic activity and can also reduce the production of MMPs by leucocytes 31. An effect on MMPs can also affect the transmigration of leucocytes into the CNS,29 thereby reducing neuro inflammation further. Various inflammatory cell subsets can disrupt CNS functions and produce toxic effects when present in the CNS in large numbers. Further, treatement with minocycline significantly amleorated dysfunction of cognition in diabetic rats. It may be working through glucose lowering mechanism, inhibition of matrix metalloproteinase ((MMP-2) & MMP-9) could be possible mechanism32.

Microglial activation in tissue culture contributes to glutamate excitotoxicity, myelin defects in neurons and reduce hippocampla neurogenesis, a process that continues in the adult brain29. The expression of several molecules associated with microglial activation, including caspase 1 (interleukin-1converting enzyme) and inducible nitric oxide synthase. Microglial expression was reduced after treatment with minocycline8 and deficient neurogenesis was also restored by the systemic administration of minocycline 33.

Apoptosis and the release of apoptotic factors is a common mechanism of neurodegeneration. Minocycline reduces apoptosis of neurons and oligodendrocytes in various neural insults34 and alleviates necrotic cell death 35. There is increasing evidence to suggest that the antiapoptotic effect is achieved through several mechanisms at the level of the mitochondrion. Minocycline stabilizes mitochondria membranes and inhibits the mitochondrial permeability transition-mediated release of cytochrome c into the cytosol36 which is a potent stimulus for the activation of caspases 9 and 3 and the induction of apoptosis. The stabilisation of mitochondrial membranes also reduces the release into the cytoplasm of other factors that trigger both caspase-dependent and caspase independent apoptotic pathways, including apoptosis inducing factor and Smac/Diablo. In cell culture, minocycline upregulates the anti-apoptotic factor Bcl-2, which then accumulates in mitochondria to antagonise the pro-apoptotic Bcl-2 family members Bax, Bak, and Bid36.

Recent research reports also indicate effectiveness of Minocycline in the experimental models of Alzheimer's disease. Minocycline has been proved beneficial in experimental model of Alzheimer's disease as shown in Passive avoidance task and elevated plus maze 37 and morris water maze38. Minocycline has also shown potent antioxidant activity as it reduced the elevated levels of several indicators of biochemical stress as well as raised the levels of several antioxidant enzymes39.

Minocycline, an antibiotic of the tetracycline family, has attracted considerable interest for its theoretical therapeutic applications in neurodegenerative diseases. However, the mechanism of action underlying its effect remains elusive. Research work40, 41 posits the intricate involvement of mitochondria in minocycline-mediated cytoprotection for neuronal cells. Following excitotoxic NMDA receptor activation, the accumulation of Ca2+ and the generation of ROS are modulated as minocycline targets mitochondria. Intervention with minocycline may prove useful as these are two events that occur early in neurodegenerative processes.Minocycline does more than just preventing Ca2+ fluxes at the plasma membrane.

It also reduced Ca2+ overload, a pivotal role in excitotoxicity and other models of cell death42-44.

Conclusion

Because of its high tolerance and excellent penetration into the brain, Minocycline has been clinically tried for neurodegenerative diseases such as stroke, spinal cord injury, epilepsy, Alzheimer's disease, ischemia and Parkinson's disease. Several intracellular signaling pathways have been implicated in the mechanism of the neuroprotective actions of Minocycline including action of Minocycline on antioxidant systems, prevention of the activation of Ca2+-dependent intracellular pathways, a marked decrease in glutamate release, blockade of the inflammatory pathway, and inhibition of molecules such as COX-2 and inflammatory mediators such as ROS and PGE2.

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