Minocycline and Cytoprotection: Shedding New Light on a Shadowy Controversy

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Abstract: In this review we explore and integrate the knowledge of the plausible pharmacological targets that could explain the new application for the well known semi-synthetic, tetracycline-derive minocycline as a cytoprotective drug. In doing so, we will analyze the possible mechanisms to elucidate the potential cytoprotective properties of minocycline. We address its anti-oxidant action ranging from its structure to its capacity to modulate the expression of oxidant-related enzymes such as nitric oxide synthase. The pharmacological targets responsible for its anti-inflammatory effects are surveyed. The effects of this antibiotic are making its marks on intracellular pathways related to neurodegenerative processes such as mitochondrial-mediated apoptosis, including minocycline-modulated effects on the expression of apoptotic proteins. Finally, we will explore the effects of minocycline on metalloproteinases, enzymes implicated in the modulation of cerebrovascular post-ischemic oxidative reperfusion injury, and new targets. In conclusion, we shed new light on the shadowy controversy of minocycline’s potential cytoprotective mechanisms and targets of action.

Keywords: Anti-inflammatory, anti-oxidant, apoptosis, cytoprotection, minocycline, mitochondria, modulation of the expression of anti-apoptotic proteins, reactive oxygen species.

INTRODUCTION

In the past few years, there has been increasing controversy concerning the effects of the tetracycline-derived antibiotic minocycline on cell survival after a cytotoxic insult [1-3]. Minocycline’s chemical structure is shown in Fig. (1). It is a second-generation tetracycline first synthesized in 1967 and commercialized in 1972. It is used in the treatment of infectious diseases including: acne vulgaris, urethritis and sexually transmitted diseases which include mycoplasmas, chlamydias and treponemas. Independent of its antimicrobial function, minocycline exerts other beneficial effects such as anti-inflammation in rheumatoid arthritis, analgesia in neuropathy pain, and in recent years its use has been proposed as a cytoprotective drug in neurodegenerative diseases. Minocycline has now been shown to confer cytoprotection in cardiovascular, renal, and nervous systems [4-11]. However, contrasting recent studies have demonstrated that minocycline treatment presented no effect or even exacerbated toxic injury in cases similar to those above referenced [12-16]. The possible causes for such different effects exhibited by minocycline remain to be determined, though minocycline has been shown to display different effects in various animal models of neurodegenerative diseases with regard to administration route, dosage, and species of animal used.

The unique properties of minocycline result in increased tissue distribution when compared to the other tetracyclines.

Of particular interest is excellent bioavailability and superior blood-brain barrier permeability to clinically effective levels because of its small size and lipophilicity [17]. The pharmacokinetics of minocycline are characterized by an excellent absorption, a long half-life, and an important, highly lipophilic property which facilitates good distribution to tissues across phospholipid membranes. The proven safety of minocycline as an antibiotic over decades of use suggests that it may hold great potential for utilizing its cytoprotective properties towards the development of an effective treatment for multiple neurological conditions in humans [18].

As with any other drug, minocycline should yield its effects after binding to a pharmacological target. Its binding to the 30S ribosomal subunit, inhibiting interaction between messenger RNA and transfer RNA and thus protein translation, is responsible for its anti-microbial action [19]. However, the mechanisms mediating the above neuroprotective effects remain elusive. In this review, we deepen the awareness of molecular and cellular targets postulated to underlie cytoprotective effects and their relevance in the field of pharmacology. We will direct our focus mainly towards cy-
toprotection within the nervous system. We believe that minocycline may exert its effects on cellular pathways via: anti-oxidant reactions, anti-inflammatory signaling pathways, mitochondrially-mediated apoptosis, and modulation of the expression of anti-apoptotic proteins (Fig. 2).

**Fig. (2).** Proposed pharmacological targets and mechanisms of minocycline.

### 1. ANTI-OXIDANT REACTIONS

The imbalance between pro-oxidants and anti-oxidants, with the former prevailing, results in oxidative stress. Reactive oxygen species (ROS), including superoxide anion radical, singlet oxygen, peroxynitrite, and hydroxyl radical are produced deleteriously by the mitochondrial electron transfer chain and by a wide variety of enzymes including monoxygenases and oxidases such as xanthine oxidase, NADPH oxidase, and cytochrome P450(s). Free radicals are implicated as causative agents in various forms of tissue destruction. ROS may interact with the lipid component of cellular membranes, initiating lipid peroxidation that results in the breakdown of the lipid constituents into highly reactive by-products [20]. Considerable evidence suggests that oxygen-based free radicals, generated as blood flow returns to formerly ischemic brain areas, are mainly responsible for the reperfusion injury that follows periods of cerebral ischemia. Oxidative stress has also been implicated in several neurodegenerative diseases including: amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig’s disease), Parkinson’s disease (PD), Alzheimer’s disease (AD) and Huntington’s disease (HD) [21].

Many of the anti-apoptotic effects of minocycline could be explained by its anti-oxidant capacity, interfering with ROS via four different proposed mechanisms:

First, using cell-free assays of anti-oxidant potency [22], data was obtained demonstrating that minocycline is a direct anti-oxidant with radical scavenging potency comparable with alpha-tocopherol. This direct property is consistent with its chemical structure (Fig. 1), which includes a multiple substituted phenol rings.

Second, a direct influence on the enzymatic complexes which lead to ROS generation. Minocycline inhibited the H2O2 level in the xanthine-xanthine oxidase and NADPH oxidase systems [23]. Furthermore, it inhibited 6-hydroxy-dopamine-induced free radical generation to decrease neurotoxicity, and also attenuated H2O2-induced neurotoxicity [24]. Minocycline also repressed some of the ROS production by zymosan-stimulated polymorphonuclear leukocytes (PMNL or PMN).

Third, through an indirect effect on the level of expression of genes implicated in ROS production. Minocycline inhibits the expression levels of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Intra-peritoneal administration reduced the increases in peptidic, amyloid-induced COX-2 expression in microglia. In primary cell culture (mesencephalon, granular cells or glia) and in brains of HD mice challenged with 1-methyl-4-phenylpyridium (MPP+), minocycline blocked the induction of iNOS. Nevertheless, minocycline failed to modify basal levels of both of the main antioxidant systems used by the cells to block ROS overproduction, glutathione and NAD(P)H, which have been shown to be modified in different neurodegenerative models [12, 25, 26].

Fourth, by an indirect mechanism due to its capacity of blocking microglia activation (see below). In the nervous system, activated microglia are the major source of NO and ROS, including H2O2 and superoxide [27, 28]. Minocycline’s inhibition of the microglial production of both NO and superoxide, and thus presumably of subsequent formation of peroxynitrite, might also serve as justification for its potential cytoprotective effects.

### 2. ANTI-INFLAMMATORY SIGNALING PATHWAYS

The inflammatory response results in the activation of various types of cells and the production of various molecules that can lead to cell death. An example of cells activated by the inflammatory response in the nervous system is microglia. It is the intrinsic immune effector cell of the central nervous system (CNS) which is normally inactive, but becomes active in the brain following a variety of debilitating events such as infection, trauma, decreased blood or oxygen flow, and neurodegenerative diseases including AD and HD. The role of microglia in the neuroinflammatory response is complex since it may involve tissue repair through the release of neutrophils and removal of necrotic debris [29], and can also release different pro-inflammatory and oxidant cytokines including interleukin-1-beta (IL-1β) and tumor necrosis factor-alpha (TNF-α). It appears that minocycline’s anti-inflammatory properties, especially its ability to suppress activation of microglia, are likely to con-
Minocycline significantly inhibited NO and prostaglandin E\(_2\) (PGE\(_2\)) production and iNOS and COX-2 expression in BV2 microglia [32]. Although minocycline is able to reduce COX-2 and iNOS expression, the effects did not reach significance in other animal models of disease such as with quinolinic acid administration to simulate HD [33].

Minocycline was very effective in protecting dopaminergic substantia nigra neurons and against the loss of reactive astrocytes. Evaluation of microglia revealed that minocycline treatment significantly reduced the lipopolysaccharide-induced activation of reactive microglia. Minocycline partially prevented the lipopolysaccharide-induced increases of mRNA levels of IL-1\(\beta\) and tumor necrosis factor-alpha (TNF-\(\alpha\)) [30]. In a model of immune-inflammatory encephalitis, minocycline reduced the release of TNF-\(\alpha\) from activated oligodendrocytes while enhancing the release of IL-10, an anti-inflammatory cytokine [34]. In addition, minocycline reduces the expression of CD11b and CD45 expression in activated microglia, minocycline significantly reduced the secretion of CD11b and CD45 expression in J20 APP-tg mice, an AD animal model. Indeed minocycline reduced the expression of CD11b and CD45 expression in J20 APP-tg mice, an AD animal model. Indeed minocycline suppressed microglial production of inflammatory (IL-1\(\beta\), IL-6, and TNF) induced by incubation with Ab42 peptide [35]. Finally, minocycline significantly reduced the secretion of both IL-6 and TNF-\(\alpha\) in microglial cells stimulated simultaneously with the peptide amyloid and serum amyloid P component (SAP) and complement factors such as C1q [36].

Thermal hyperalgesia and tactile allodynia develop in response to sciatic nerve ligation. Recent data strongly support the idea that spinal cord microglia activation and proliferation contribute directly to such neuropathic pain-like states in mice, an effect that can be prevented by using minocycline to inhibit microglial activation [37]. In line with this study, Hains and Waxman [38] have shown that phosphorylated-p38 MAP kinase upregulation is concomitant with the activation of microglia within the lumbar dorsal horn after traumatic spinal cord injury. Levels of phosphorylated-p38 and microglia activation were decreased in animals receiving minocycline, while cessation of delivery of minocycline resulted in an immediate return of pain-related phenomena.

Finally, it has been shown that minocycline protects against neurotoxicity in the serotonergic and dopaminergic systems in the brains of monkeys and mice treated with the amphetamine derivatives methamphetamine or 3,4-methylenedioxyamphetamine (MDMA, “ecstasy”), an effect apparently mediated by inhibition of microglia activation [39-41; but see 42]. However, a broad range of evidence indicates that dopamine-derived free radical formation plays an important role in methamphetamine- and MDMA-induced neurotoxicity [43]. Accordingly, it could also be speculated that the cytoprotective effects of minocycline could be due to its anti-oxidant properties (see above) or to the prevention of dopamine-derived pro-oxidant species since minocycline attenuates the acute dopamine release induced by methamphetamine [40].

3. MODULATION OF INTRACELLULAR PATHWAYS

Second messengers transmit signals from extracellular agents to modify intracellular processes. They typically regulate cellular functions by modulating the phosphorylation state of intracellular proteins. Protein kinases and phosphatases typically act either on the serine or threonine residues (Ser/Thr kinases or phosphatases) or the tyrosine residues (Tyr kinases or phosphatases) of their substrates. The phosphatidylinositol-3-kinase (PI3K) pathway has emerged as one of the critical factors in anti-apoptotic signal transduction. Its activation is known to protect cells from several apoptotic stimuli [44, 45]. The neuroprotective effects of minocycline were blocked by PI3K inhibitors LY294002 and wortmannin in some models including glutamate-induced apoptosis in cerebellar granular cells where minocycline maintained the activity of the PI3-K/Akt pathway [46].

Minocycline’s cytoprotective effects have also been attributed to its capacity to block enzymatic activity of mitogen-activated protein kinases (MAPKs). The MAPKs, including the extracellular-signal regulated kinases (ERKs), are normally inactive in neurons but become activated when they are phosphorylated by other kinases. Activated MAPKs can phosphorylate transcription factors, proteins that regulate gene expression. The ERK (p42/p44 MAPK) cascade is thought to play a pivotal role in the integration and transmission of transmembrane signals required for growth and differentiation. The activity of the pathway is often represented by the levels of MEK-phosphorylation of ERK1 and ERK2. Minocycline blocked the activation of p38 MAPK induced by different stimuli such as NO [47], 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and the up-regulation of glutamate-family receptors by NMDA agonists or glutamate. Its neuroprotective effects on bilirubin-induced cerebellar hypoplasia in the Gunn rat, a genetic model of hyperbilirubinemia, may be due in part to an inhibition of p38 MAPK activity [48]. Furthermore, minocycline’s cytoprotective effects on gentamicin-induced ototoxicity are mediated by the inhibition of p38 MAPK activation [49].

To ascertain the mechanism of minocycline inhibition of MAPKs, Nikodema et al., used various stimuli to activate the MAPK signaling pathways including H\(_2\)O\(_2\) and BzATP, a P2X7 purinergic receptor agonist, which strongly activated p38, ERK1/2 and JNK1/2 MAPKs in murine BV-2 microglia cells. Under these conditions, minocycline was surprisingly unable to inhibit the activation of any of the MAPKs in response to stimulation with H\(_2\)O\(_2\). Moreover, minocycline had differential effects on BzATP-stimulated MAPKs; ERK1/2 and JNK1/2 activation was significantly decreased, whereas p38 activation was not affected [50].

Minocycline was able to inhibit p38 MAPK in microglia and that specific inhibition of p38 MAPK, but not p44/42 MAPK, provided neuroprotection against NMDA toxicity and prevented microglial proliferation [6]. p38 MAPK is thought to mediate inflammatory responses in various cell types [51, 52], including microglia [53]; therefore, inhibition of p38 MAPK may be beneficial in injuries involving inflammation and microglial activation. Several studies with
specific inhibitors of p38 MAPK have proved to be neuroprotective and provide anti-inflammatory effects [53-56]. Another MAPK family member, p44/42, is stimulated by extracellular mitogens and is involved in proliferation and differentiation of several cell types, thereby supporting cellular survival [57]. In agreement with the survival supporting role of p44/42 MAPK, Sugino et al. [55] did not observe neuroprotection against transient brain ischemia by inhibiting p44/42 MAPK, and in the present study inhibition of p44/42 MAPK slightly increased NMDA-induced neuronal death rather than being protective. However, p44/42 has also been shown to contribute to ischemic neuronal death in vivo [58] and in vitro, indicating that the role of p44/42 MAPK may depend on the injury model, timing, and dosing of the inhibitor treatment.

4. INHIBITION OF MITOCHONDRIAL APOPTOTIC PATHWAYS

Mitochondria are being considered the main link between cellular stress signals activated during acute and chronic nerve cell injury and the execution of programmed nerve cell death [59]. In most vertebrates, the pivotal event in apoptotic processes involves increased permeability of the outer mitochondrial membrane (OMM), resulting in the release of a variety of proteins normally resident in the mitochondrial intermembrane space. The prodigious prospects for the neuroprotective effects of minocycline could be attributed to those reports demonstrating that minocycline blocks the opening of the mitochondrial high-conductance permeability transition pore (PTP). The formation of the PTP is a key step in cellular programs associated with cell death situations. This process can trigger the mitochondrial release of cell death-inducing factors including: cytochrome c, second mitochondrial-derived activator of caspase (SMAC), direct inhibitor-of-apoptosis protein-binding protein with low pI (DIABLO), and apoptosis-inducing factor (AIF) [60].

Several studies, including our own, have shown that minocycline proves effective in blocking mitochondrial swelling when the stimulus is calcium [13, 61]. Indeed, minocycline might have distinct mechanisms of action against oxidative (tert-butyl hydroperoxide, phenylarsine oxide) and cycline might have distinct mechanisms of action against ling when the stimulus is calcium [13, 61]. Indeed, minocycline proves effective in blocking mitochondrial swelling rather than being protective. However, p44/42 has also been shown to contribute to ischemic neuronal death in vivo [58] and in vitro, indicating that the role of p44/42 MAPK may depend on the injury model, timing, and dosing of the inhibitor treatment.

5. MODULATOR EFFECTS ON THE EXPRESSION OF APOPTOSIS-RELATED PROTEINS

Gene expression is involved in many cell death programs probably because many cellular responses to environmental changes are mediated by inducible transcription factors such as nuclear factor xB (NFxB) and p53. Interfering with the activity of transcription factors can have profound effects on cell fate. Minocycline was shown to inhibit NFxB binding to DNA in HIV-1-infected microglia [67], and to prevent the lipopolysaccharide-induced degradation of the NFxB inhibitor IxBs subunit. These findings suggest that minocycline may reduce the translocation of NFxB to the nucleus, resulting in decreased transcriptional activity [50].

The p53 tumor suppressor gene is a sequence-specific transcription factor that activates the expression of genes in charge of promoting growth arrest or cell death in response to multiple forms of cellular stress. In the mature nervous system, numerous studies indicate that p53 plays a key role in neuronal death following a certain number of insults [68, 69]. Recently, Kelly et al. reported that minocycline was able to block the up-regulation of p53 in a rat model of ischemic renal injury [70].

The Bcl-2 family of proteins governs the mitochondria-dependent pathway for apoptosis [63-65]. Bcl-2 is a key molecular determinant of minocycline-mediated protection. The ratio between anti- and pro-apoptotic molecules determines cell fate, such that relatively elevated levels of Bcl-2 favor cell survival while relatively elevated levels of Bax promote cell death. Induction of the anti-apoptotic protein Bcl-2 by minocycline could be one possible mechanism to explain the cytoprotection conferred by this drug. Minocycline was able to induce mitochondrial Bcl-2 accumulation and interaction with apoptosis-promoting factors such as Bax, Bak and Bid. Interestingly, the down-regulation of Bcl-2 expression by anti-sense oligonucleotides abolished the neuroprotective effects of minocycline [71].

The interaction of X chromosome-linked inhibitor-of-apoptosis protein (XIAP) with SMAC/DIABLO contributes to the regulation of apoptosis in several models. Minocycline decreased the caspase levels and increased the relationship between XIAP and SMAC/DIABLO. This synergistic action strongly prevented the induction of caspase activity which is typically associated with post-ischemic and oxidative reperfusion damage [72]. Moreover, minocycline treatment reduced the translocation of SMAC/DIABLO from the mitochondria into the cytosol, similar to its effects on cytochrome c translocation.

The cysteine protease family members, of which the caspases and calpains are the best representatives, play essential roles in the induction, transduction, and amplification of intracellular apoptotic signals as seen in the pathogenesis.
of numerous CNS disorders [73]. There are two types of caspases: initiator caspases and effector caspases. Initiator caspases (e.g. caspase-8, caspase-9) cleave inactive pro-forms (pro-caspases) of effector caspases, thereby activating them. Effector caspases (e.g. caspase-3, caspase-7) in turn cleave other protein substrates within the cell, resulting in the promotion of apoptotic processes. Activation of these cell death proteases after injury might occur in neurons or glial cells, such as astrocytes and microglia. Caspase-3 is an executor caspase that is responsible for cleaving a variety of substrates that lead to the morphological features of apoptosis. Minocycline inhibits the activation of caspase family members through a double mechanism. First, by blocking the release of cytochrome c from the mitochondria, minocycline avoids the formation of the apoptosomal, multi-protein complex required for the activation of caspase-9 and later caspase-3. Second, minocycline might modulate the expression, and thus it is able to reduce the expression of caspase-1 and caspase-3 mRNA in a transgenic mouse model of HD [74].

6. MODULATION IN CEREBROVASCULARATURE

Alterations in properties of the cerebrovasculature have been suggested as contributing to the potential pathogenesis in neurodegenerative diseases [75, 76]. For example, impaired cerebral circulation, vascular inflammation, and blood-brain barrier (BBB) dysfunction have been identified in the brains of AD patients [77]. The functional importance of the cerebrovasculature in AD is based on its ability to maintain a homeostatic environment, crucial to the viability of neurons [78]. Minocycline exhibits anti-angiogenic properties comparable to that of the combination of heparin and cortisone [79], and it has been proposed as a candidate therapeutic compound to inhibit cerebrovascular alterations in AD [80].

Matrix metalloproteinases (MMP) activity increases BBB permeability. Minocycline attenuates adaptive immunity by reducing the expression and activity of MMP, thereby reducing T-cell migration into the CNS, and thus preventing T cell-mediated myelin degradation. MMP is a family of zinc-dependent proteases responsible for the extracellular matrix turnover and degradation of bioactive proteins. In cerebral ischemia, MMPs 2 and 9 have been identified as mediators of the degradation of the basal lamina [81, 82] and hemorrhagic transformation [83]. Interference of this cascade by minocycline might be a participative pathway for neurovascular protective properties. Minocycline presents higher inhibitory effects on MMP-9 than on MMP-2 under both in vivo [84] and in vitro [85] conditions. MMPs require zinc in their active site for functional activity, and removal of the zinc leads to a change in conformation with resultant inactivation of the enzyme. To explain these inhibitory effects, a double mechanism that implies its ability to chelate divalent ions and the down-regulation of gene expression [86] has been proposed.

7. OTHER PLAUSIBLE MECHANISMS OF ACTION

Besides of the above explained mechanisms, an inhibitory effect of minocycline on aggregate protein formation has been previously described. Tetracycline and its derivatives are claimed to bind amyloid fibrils generated by synthetic peptides of human PrP and human Ab1-42/Ab1-40, and reduce the formation of amyloid fibrils by these peptides [87, 88]. Although the mechanisms are not fully understood, polar interactions and the formation of hydrogen bonds are suggested to be the possible molecular basis for binding of tetracycline to fibrillogenic structures.

Minocycline is a strong inhibitor of huntingtin, a protein vital to protein aggregate formation in slices of hippocampus in HD models. However, important differences between abnormal behavior and the number of aggregates were not observed in post-mortem animal necropsies.

Finally minocycline has been shown to inhibit the poly(ADP-ribose) polymerase-1 (PARP-1) [89], an enzyme that when activated by DNA damage promotes both cell death and inflammation. Alano et al. have reported that minocycline is able to block PARP-1-mediated neuronal death in culture by directly inhibiting PARP-1 activity.

CONCLUSION

The present review study adds an updated overview of the plausible targets that can be modulated by minocycline. It is a safe antibiotic in clinical use that in the past few years has been proposed for use as a cytoprotective drug. However, not all results support minocycline as a proper tool to help fight against neurodegenerative diseases. There have been published reports about phenotypic models of PD and HD in monkeys and rats in which minocycline treatment actually increased toxic effects and produced a great loss of dopaminergic nerve endings. What accounts for the seemingly contradictory effects of minocycline on neuronal cell survival following acute injury? These differences in outcome resulting from the above target modulations may depend not only upon the nature and severity of injury, but also the cell type activated [2, 90]. By inhibiting microglia, minocycline could be blocking repair mechanisms. Additionally, the negative effects of minocycline on the respiratory states of CNS mitochondria are likely not compatible with the high energy demand of neuronal cells, and could contribute to the neurotoxicity of minocycline in animals and humans at high doses as suggested elsewhere [62]. As expected in neurodegenerative disease, any of the aforementioned detrimental cascades could be activated to result in programmed cell death. Furthermore, several of them may be mediating these apoptotic processes in a simultaneous and parallel fashion. If some of these pathologic cascades by-pass minocycline-induced cytoprotective effects, neuronal death may still be unavoidable. For this reason, more data from experimental conditions are required to elucidate all of the pathways relevant to neurodegenerative disease, as well as to determine the most appropriate dosage, route of administration, and therapeutic window in which minocycline yields neuroprotection.

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LIST OF ABBREVIATIONS

MPTP = 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPP' = 1-Methyl-4-phenylpyridium
AD = Alzheimer disease
ALS = Amyotrophic lateral sclerosis
AIF = Apoptosis-inducing factor
BBB = Blood-brain barrier
CNS = Central nervous system
COX-2 = Cyclooxygenase-2
DIABLO = Direct inhibitor-of-apoptosis protein-binding protein with low PI
ERKs = Extracellular-signal regulated kinases
HD = Huntington disease
iNOS = Inducible nitric oxide synthase
IL = Interleukin
MMP = Matrix metalloproteinases
MAPKs = Mitogen-activated protein kinases
NGF = Nerve growth factor
NFkB = Nuclear factor kB
OMM = Outer mitochondrial membrane
PD = Parkinson’s disease
PTP = Permeability transition pore
PI3K = Phosphatidylinositol-3-kinase
PARP-1 = polyADP-ribose polymerase-1
PMNL or PMN = Polymorphonuclear leukocytes
PGE2 = Prostaglandin E2
ROS = Reactive oxygen species
SMAC = Second mitochondria-derived activator of caspase
SAP = Serum amyloid P component
TNF-α = Tumor necrosis factor-alpha
XIAP = X chromosome-linked inhibitor-of-apoptosis protein

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Minocycline and Cytoprotection

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