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HIGH IMPACT REVIEW IN NEUROSCIENCE, NEUROLOGY OR PSYCHIATRY - REVIEW ARTICLE

Tetracycline repurposing in neurodegeneration: focus on Parkinson's disease

Mariza Bortolanza[1,2] · Glauce C. Nascimento[1,2] · Sergio B. Socias[3] · Diego Ploper[3] · Rosana N. Chehín[3] · Rita Raisman-Vozari[4] · Elaine Del-Bel[1,2]

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Abstract

The prevalence of Parkinson's disease, which affects millions of people worldwide, is increasing due to the aging population. In addition to the classic motor symptoms caused by the death of dopaminergic neurons, Parkinson's disease encompasses a wide range of nonmotor symptoms. Although novel disease-modifying medications that slow or stop Parkinson's disease progression are being developed, drug repurposing, which is the use of existing drugs that have passed numerous toxicity and clinical safety tests for new indications, can be used to identify treatment compounds. This strategy has revealed that tetracyclines are promising candidates for the treatment of Parkinson's disease. Tetracyclines, which are neuroprotective, inhibit proinflammatory molecule production, matrix metalloproteinase activity, mitochondrial dysfunction, protein misfolding/aggregation, and microglial activation. Two commonly used semisynthetic second-generation tetracycline derivatives, minocycline and doxycycline, exhibit effective neuroprotective activity in experimental models of neurodegenerative/ neuropsychiatric diseases and no substantial toxicity. Moreover, novel synthetic tetracyclines with different biological properties due to chemical tuning are now available. In this review, we discuss the multiple effects and clinical properties of tetracyclines and their potential use in Parkinson's disease treatment. In addition, we examine the hypothesis that the anti-inflammatory activities of tetracyclines regulate inflammasome signaling. Based on their excellent safety profiles in humans from their use for over 50 years as antibiotics, we propose the repurposing of tetracyclines, a multitarget antibiotic, to treat Parkinson's disease.

Keywords Doxycycline · Antibiotic · Drug repurposing · Neuroprotection · Parkinson's disease · Tetracycline

Introduction

Patients with Parkinson's disease (PD), which is a chronic neurological disorder caused by the loss of dopaminergic neurons in the substantia nigra pars compacta and their terminals in the striatum, exhibit decreased striatal dopamine, which results in the classical PD motor symptoms of bradykinesia, rigidity, and tremor. Nondopaminergic

Mariza Bortolanza and Glauce Crivelaro-do-Nascimento contributed equally to the review.

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✉ Rita Raisman-Vozari
ritaraisman@gmail.com

✉ Elaine Del-Bel
eadelbel@usp.br

[1] Department of Morphology, Physiology and Basic Pathology, Faculty of Odontology of Ribeirão Preto, University of São Paulo (USP), Av do Café s/n, São Paulo, Brazil

[2] Center of Interdisciplinary Research on Applied Neurosciences (NAPNA), USP, São Paulo, Brazil

[3] Instituto de Investigación en Medicina Molecular y Celular Aplicada (IMMCA) (CONICET/UNT/SIPROSA), Pasaje Dorrego, 1080-4000 Tucumán, Argentina

[4] Sorbonne Universite, UPMC Univ Paris 06, INSERM, CNRS, UM75, U1127, UMR 7225, Institut du Cerveau et de la Moelle Epinière, Paris, France

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neurons also degenerate during the evolution of the disease and account for the dopamine-resistant symptoms, including olfactory dysfunction, autonomic dysfunction, sleep disorder, pain, and sensory problems (Rodríguez-Violante et al. 2017). Several factors at the cellular level are thought to underlie the neuronal demise in PD. These include oxidative stress, mitochondrial and lysosomal dysfunction, apoptosis, the formation of a pathologic species of aggregated α-synuclein protein, and inflammatory changes (Bi et al. 2013; Olanow 2007). Thus, PD clearly involves multifactorial characteristics.

PD has an inflammatory component, which has been confirmed by postmortem brain studies of patients with PD, serum and cerebrospinal fluid cytokine analyses, and examinations of risk factor associations with cytokine and major histocompatibility complex polymorphisms (Frank-Cannon et al. 2009; Hirsch and Hunot 2009; Lee et al. 2009; Tansey and Goldberg 2010). Epidemiological studies of anti-inflammatory therapies (Hirsch and Hunot 2009; McGeer and McGeer 2008) have indicated a reduced risk of PD among long-term users of nonsteroidal anti-inflammatory drugs (Chen et al. 2003; Ton et al. 2006). However, the results of anti-inflammatory therapies are inconsistent as some nonsteroidal anti-inflammatory drugs have been shown to exacerbate neurodegeneration (Lleo et al. 2007). Moreover, anti-inflammatory efficacy has not been reproduced in all clinical trials (Bartels et al. 2010). These findings suggest that multitarget drugs are more appropriate than treatment with anti-inflammatories alone.

Consistent with the multifactorial origin of PD, pathogenic interactions among the diverse pathologic mechanisms underlying the development of the disease have been proposed to enhance neuronal death. Thus, the release of aggregated α-synuclein from neurons might activate microglia and trigger the production of proinflammatory mediators and neurotoxic factors, which then lead to neuronal damage (Codolo et al. 2013; Santa-Cecilia et al. 2016). Among these proinflammatory mediators is interleukin (IL)-1 beta (IL-1β), which is one of the most abundant and strongest proinflammatory cytokines (Codolo et al. 2013). The synthesis of IL-1β is induced by fibrillar α-synuclein through an interaction with the toll-like receptor-2. Furthermore, IL-1β secretion involves the activation of the nucleotide-binding domain and leucine-rich repeat-containing family, pyrin domain-containing-3 (NLRP3) inflammasome (Codolo et al. 2013).

Inflammasomes are multiprotein complexes that play a central role in inflammatory immune responses. They are primed by the mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF-κB) pathways and activated by several damage-associated molecular patterns and pathogen-associated molecular patterns (Kauppinen et al. 2013). Inflammasomes are critical in regulating the maturation of the proinflammatory IL-18 and IL-1β (Codolo et al. 2013; Lin and Zhang 2017). Interestingly, Codolo et al. (2013) have found that only fibrillar α-synuclein induces the release of IL-1β by monocytes after activation of the NLRP3 inflammasome.

Unfortunately, only symptomatic treatments are available for PD, and no cure nor disease-modifying drug currently exists (Kowal et al. 2013). Although several pharmacological compounds improve nigrostriatal pathway function and alleviate the motor and nonmotor symptoms of the disease, these compounds do not slow disease progression (Schapira 2005). Indeed, the effects of dopamine replacement therapy with L-3,4-dihydroxyphenylalanine (L-DOPA), which is the most efficient treatment of the PD motor symptoms (Fahn 2008; Olanow 2008), tend to decrease with time. Longer L-DOPA treatments are accompanied by motor and/or psychiatric side effects that are extremely discomforting for the patients. Therefore, future drug research and development must focus on finding compounds that slow dopaminergic neurodegeneration and impede illness progression (LeWitt and Nyholm 2004; Schapira et al. 2006). Despite the huge efforts and resources already invested, the development of new neuroprotective drugs has high rates of failure. In fact, several promising drugs have failed once they reached clinical trials mainly due to safety issues, including unexpected clinical side effects and/or tolerability (Ashburn and Thor 2004; Cha et al. 2018). Therefore, drug repurposing might be useful for overcoming this bottleneck in PD treatment by avoiding future derailments due to appearance of toxicities that were not predicted by the preclinical research.

In addition to their antimicrobial properties, tetracyclines are antibiotics that may protect against neurodegenerative (Blum et al. 2004; Forloni et al. 2009; Noble et al. 2009a, b; Ruzza et al. 2014; Stoilova et al. 2013) and neuropsychiatric (Keller et al. 2013) diseases. These drugs exhibit an array of brain protective functions (Gordon et al. 2012; Moon et al. 2012), including the reduction of neuroinflammatory processes (Gordon et al. 2012; Noble et al. 2009a, b; Nordstrom et al. 1998; Sultan et al. 2013) and prevention of mitochondrial-mediated cytochrome c release, glutamate neurotoxicity, and oxidative stress (Kim and Suh 2009; Mao et al. 2005; Rothstein et al. 2005; Tomiyama et al. 1996a). In addition, they are effective inhibitors of metalloproteinases (Cathcart and Cao 2015; Cho et al. 2009; Lee et al. 2009), tumor progression (Amin et al. 1997), and angiogenesis induction (Furst 1998). Importantly, subantimicrobial doses of tetracyclines have been successfully used for the treatment of acne vulgaris, rosacea, and periodontal disease without serious side effects on the patient's health, which suggests the safety of antibiotic therapy (Skidmore et al. 2003). Interestingly, Egeberg et al. (2016) have reported that increased tetracycline use in rosacea treatment is associated with a small but appreciable reduction in the risk of developing PD,

which suggests that tetracyclines have potential for treating PD.

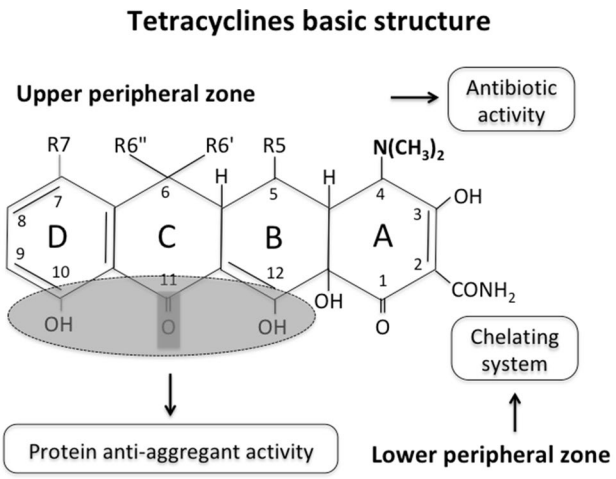
Clinically, the off-target effects of drugs are critically important. Drug repositioning or repurposing is an attractive alternative (Ashburn and Thor 2004; Johnston et al. 2018; Stock et al. 2013) to de novo drug development. Specifically, drug repositioning reduces development risk because repositioning candidates have usually already been through several stages of clinical development and therefore have well-known safety and pharmacokinetic profiles (Papapetropoulos and Szabo 2018). De novo drug discovery and development, which begins with an idea and continues until the drug is marketed, is a 10–17-year process (Ashburn and Thor 2004; Cha et al. 2018). Thus, drug repurposing may be key for the faster development of neuroprotective treatments against PD.

The aim of the present review was to carefully compile evidence of the potential effects of tetracyclines in the treatment and/or prevention of PD. Here, we briefly examine the chemical structure, mechanisms of action, and properties of tetracyclines that may result in neuroprotection. Finally, we will summarize the available data on the preclinical and clinical testing of tetracyclines.

The structure–activity relationship of tetracycline

Tetracycline, which is a natural fermentation product of the soil bacterium *Streptomyces aureofaciens* was discovered by Benjamin Duggar in (1948). The first tetracycline to be chemically purified was chlortetracycline in 1954 (Griffin et al. 2010; Sapadin and Fleischmajer 2006). The mechanisms of action underlying the antibiotic properties of tetracyclines are related to their ability to bind to the bacterial 30S ribosomal subunit, which then halts protein translation. Upon binding to the ribosome, tetracyclines allosterically inhibit the binding of the amino acyl-tRNA at the acceptor site, which then prevents assembly of the translational machinery (Connamacher and Mandel 1965; for review, see; Nelson and Levy 2011).

Currently, the following three groups of tetracyclines exist: tetracycline natural products, tetracycline semisynthetic compounds, and chemically modified tetracyclines (CMTs; Golub et al. 1992; Nelson 1998; for review, see; Swamy et al. 2015). All tetracyclines consist of a linear-fused tetracyclic nucleus (rings designated a–d in Fig. 1), which is an important feature in its antibacterial activity. The ring structure is surrounded by upper and lower peripheral zones that contain various chemical functional groups (Martin 1985). The dimethylamine group at the C4 carbon on the upper half is necessary for its antimicrobial activity (Fig. 1). Interference with this region reduces or eliminates



TETRACYCLINES	Radical			
	R5	R6'	R6"	R7
Tetracycline	H	OH	CH_3	H
Doxycycline	OH	H	CH_3	H
Minocycline	H	H	H	$N(CH_3)_2$
CMT-3	-	-	-	-

Fig. 1 Chemical structure and activity relationship of tetracycline, DOX, MIN and CMT-3. Tetracycline molecules are all comprised by a linear-fused tetracyclic nucleus (rings designated **a–d**), an important feature for the antibacterial activity. Modifying the upper peripheral zone (positions C7 through C9 of the D ring) led to the synthesis of molecules with higher activity. The lower peripheral region contains functional groups that are responsible for inhibition of protein aggregation and chelation of metal ions. This feature has an influence on both their antimicrobial and pharmacokinetic properties (Socias et al. 2018; for review see; Bahrami et al. 2012; Chopra and Roberts 2001). Modification of the lower peripheral region reduces both antibiotic and nonantibiotic properties (Nelson 1998)

the effectiveness of the drug as an antibiotic (Golub et al. 1998). The lower peripheral region contains functional groups that are responsible for the chelation of metal ions (Fig. 1; Bahrami et al. 2012).

Chemical modifications have produced the following two newer semisynthetic second-generation tetracyclines: 6-deoxy-5-hydroxytetracycline [doxycycline (DOX)] and 7-dimethylamino-6-demethyl-6-deoxytetracycline [minocycline (MIN)]. DOX and MIN, which are most commonly used clinically as antibiotics, are characterized by reduced toxicity, enhanced antibacterial activity, longer half-lives, superior tissue fluid penetration, easier penetration of the blood–brain barrier (Domercq and Matute 2004), and rapid and complete absorption, even in aging individuals (Sande and Mandell 1985). DOX is indicated for a variety of infections, including anthrax, chlamydia, community-acquired

pneumonia, Lyme disease, cholera, syphilis, Yersinia pestis (plague), periodontal infections, severe acne, and malaria. MIN, which is used more often, also displays broad-spectrum efficacy and is indicated for many of the same infections as DOX (Joshi and Miller 1997). However, the effects of MIN and DOX in the central nervous system are not fully understood nor have they been characterized.

A new family of interesting CMT compounds has been chemically modified to eliminate their antimicrobial activities while retaining their anticollagenase activities (Golub et al. 1992, 1998, 1999). Currently, more than eight CMTs are available (Gu et al. 2011). Among them, CMT-1, CMT-3, and CMT-8 have been tested in medical applications. CMT-3 [6-demethyl-6-deoxy-4-de(dimethylamino)-tetracycline] is the only CMT that has been tested in clinical trials on cancer patients (Agnihotri and Gaur 2012). CMTs do not produce major side effects compared to antimicrobial tetracycline therapy, and their administration in experimental animals does not produce tetracycline-resistant microorganisms in the oral and gut flora (Golub et al. 1991).

The pleiotropic properties of CMT-3 provide impressive therapeutic potential for reducing excessive connective tissue breakdown during various pathologic processes, including those in inflammatory diseases (Chu et al. 2007; Dezube et al. 2006; Fingleton 2003; Greenwald 1998). CMT-3 inhibits lipopolysaccharide (LPS)-induced microglia activation and cytokine expression in the brain (Edan et al. 2013). Because CMT-3 is highly lipophilic, it is expected to cross the blood–brain barrier and therefore affect cells within the brain (Chen et al. 2000; Edan et al. 2013).

The nonantimicrobial properties of tetracyclines

A wide spectrum of effects of tetracyclines in the nervous system can be attributed to their nonantibiotic properties (Sapadin and Fleischmajer 2006). These properties are listed below.

Matrix metalloproteinase (MMP) inhibition

MMPs are produced by inflammatory and connective tissue cells. The inhibition of MMPs is beneficial in many pathological conditions in which the MMP-mediated proteolysis of the extracellular matrix contributes to inflammation, which has been shown in animal model studies of stroke, neurodegeneration, neuroimmunity, and neuroinfection (Plane et al. 2010). Tetracyclines are thought to exert their antiproteolytic effects both through the direct inhibition of MMPs activity and the inhibition of their expression (Griffin et al. 2010). Because MMP transcription is induced by numerous proinflammatory cytokines and growth factors, including IL-1, IL-6, tumor necrosis factor-alpha (TNF-α), and epidermal growth factor, the upstream signaling cascades that induce MMP expression are probably important targets of tetracyclines (Hanemaaijer et al. 1998).

Reactive oxygen species (ROS) scavenging

The increased production of ROS under many pathological conditions results in oxidative destruction or the dysfunction of many cellular constituents. The neuroprotective roles of DOX and MIN have been attributed to their ability to scavenge ROS and free radicals (Bahrami et al. 2012; Garcia-Martinez et al. 2010; Nikodemova et al. 2006; Plane et al. 2006). MIN has been shown to directly scavenge ROS in several cell-free mixed-radical assays (Kraus et al. 2005). Additionally, MIN is very effective for quenching H_2O_2 and scavenging superoxide and peroxynitrite through direct interactions with these free radicals (Kraus et al. 2005; Whiteman and Halliwell 1997).

MIN and DOX inhibit oxidative stress by also attenuating the expression of inducible nitric oxide (NO) synthase (iNOS; Amin et al. 1997). NO reacts with oxygen radicals and forms cytotoxic species, such as peroxynitrite. Tetracyclines can act on this enzyme at the transcriptional and/or translational level, which accounts for the observations of decreased protein levels and specific activity of the enzyme and the subsequent reduction in NO production (Amin et al. 1997; DeClerck et al. 1994; Rifkin et al. 1994).

Antiapoptotic effects

A key event in the execution of the apoptotic cascade is the activation of caspases, which are a family of cysteine proteases. Tetracyclines possess antiapoptotic properties that result in reductions in the expression of caspase-1 and/or caspase-3. In addition, MIN enhances the effects of B-cell lymphoma-2 (Bcl-2), which protects cells against apoptosis (Jordan et al. 2007; Wang et al. 2010).

Anti-inflammatory effects

The downregulated expression of proinflammatory mediators is a well-characterized and common effect of all tetracyclines, especially MIN and DOX (Golub et al. 1998). Reports have shown that tetracycline, DOX, and MIN decrease inflammations of various etiologies (Bahrami et al. 2012). Thus, tetracyclines attenuate both innate and adaptive immune responses (Griffin et al. 2010).

MIN and DOX exert their anti-inflammatory effects in the brain by modulating glial cells. Microglial activation occurs in most neurodegenerative diseases and results in the release of proinflammatory mediators and other injury response factors that compromise cell viability (Domercq and Matute

2004). By reducing microglial activation, tetracyclines reduce the transcription of downstream proinflammatory mediators, such as caspase-1, iNOS, and cyclooxygenase 2, and the subsequent release of IL-1β, NO, and prostaglandin E_2, which are associated with neuronal cell death (Domercq and Matute 2004; Orsucci et al. 2009). In addition, MIN attenuates the p38 MAPK cascade, which reduces inflammatory cytokine synthesis (Bahrami et al. 2012; Tikka and Koistinaho 2001; Wu et al. 2002; Yrjanheikki et al. 1998).

MIN and, to a lesser extent, DOX inhibit phospholipase A_2 (Pruzanski et al. 1992) and neutrophil migration (Esterly et al. 1984) and adherence (Gabler and Creamer 1991). In addition, DOX reduces mitogen-induced proliferative responses of lymphocytes (Thong and Ferrante 1979).

Furthermore, DOX (Cox et al. 2010) and MINO (Tamargo et al. 1991) inhibit angiogenesis, which occurs also in neurodegenerative diseases (for review see Bradaric et al. 2012).

Regarding the neuroinflammation induced by α-synuclein, Codolo et al. (2013) have suggested that blocking IL-1β activity may be a valuable alternative to reducing and/or stopping α-synuclein-triggered immune responses because this cytokine is the final product of the NLRP3 inflammasome. Thus, DOX exerts strong anti-inflammatory actions on microglial cells and ceases the production of inflammatory mediators by suppressing the NF-κB and p38 MAPK pathways. Moreover, DOX strongly restricts the production/release of IL-1β and TNF-α (Santa-Cecilia et al. 2016) and diminishes the increase in TNF-α and IL-1β mRNA transcripts observed in LPS-stimulated BV-2 cells (Cho et al. 2009).

Protein antiaggregation activity

Neurodegenerative diseases can be classified according to their predominant protein aggregates (Maiti et al. 2014). An important hallmark of neurodegenerative disorders, including PD and Alzheimer's disease, is the intraneuronal (tau or α-synuclein) and extracellular [amyloid beta (Aβ) peptide] accumulation of misfolded proteins. The evidence suggests that α-synuclein is involved in the pathogenesis of several disorders through the promotion of the fibrilization of tau and Aβ as well as the phosphorylation of tau (Wong and Krainc 2017).

In the postmortem brains, specifically the substantia nigra and striatum, of patients with PD, increased α-synuclein accumulation has been observed in mitochondria (Subramaniam et al. 2014). In turn, the mitochondrial dysfunction caused by α-synuclein might induce the enhanced production of ROS, which appears to modulate α-synuclein oligomerization and cytotoxicity (Brahmachari et al. 2016). Recently, Socias et al. (2018) have analyzed the antiamyloidogenic effects of different antibiotics on well-known disease-associated proteins. Their results suggested that a specific structural motif in tetracyclines is key for the inhibition of protein amyloid aggregation (Socias et al. 2018) and that the oxidation products of antibiotics with additional hydroxyl groups on their rings further inhibit α-synuclein fibrillation (Fig. 1). DOX also induces the remodeling of α-synuclein oligomers into off-pathway nontoxic and non-seeding species. Interestingly, this remodeling process is only effective on the early species in the aggregation process (González-Lizárraga et al. 2017).

Protection against mitochondrial dysfunction

Mitochondrial dysfunction has also been implicated in multifactorial age-related diseases, including PD (Andreux et al. 2013). Garcia-Martinez et al. (2010) have postulated that mitochondria are pharmacological targets of MIN. When MIN is added to isolated mitochondria, it decreases the mitochondrial inner membrane potential, which might prevent mitochondrial permeability, transition pore opening, and the subsequent release of cytochrome c. In addition, MIN decreases the voltage dependence in a concentration-dependent manner, which alters the permeability of the mitochondrial outer membrane (Garcia-Martinez et al. 2010). These transmembrane potential changes might contribute to the various cytoprotective mechanisms described above.

The pituitary adenylate cyclase-activating polypeptide (PACAP), histone methylation, and poly (ADP-ribose) polymerase-1 (PARP-1): new targets for the neuroprotective effects of tetracyclines?

The pituitary adenylate cyclase-activating polypeptide receptor 1 (PAC1R) is located in the central and peripheral nervous systems, in which it mediates antiapoptotic (Seaborn et al. 2011), anti-inflammatory (Martínez et al. 2006), and neuroprotective (Bourgault et al. 2009) effects. DOX, which is a positive allosteric modulator of PAC1, enhances the activation of this receptor in vivo (Yu et al. 2016). Therefore, PAC1 may be the source of yet another neuroprotective function of DOX, which suggests that the anti-inflammatory effects of DOX interact with the functions of PAC1 (Reglodi et al. 2017).

The activation of PARP-1 by DNA damage promotes both cell death and inflammation. Alano et al. (2006) have reported that the enzymatic activity of PARP-1 is directly inhibited by MIN, DOX, and other tetracycline derivatives that have neuroprotective and anti-inflammatory actions. The neuroprotective and anti-inflammatory effects of tetracycline derivatives may be attributable to PARP-1 inhibition, particularly under conditions in which cell death is mediated primarily by PARP-1 activation. MIN has a beneficial effect on DNA damage, which might be due to its ability to inhibit

PARP-1 activation. In addition, MIN might regulate the levels of histone methylation, which is partially explained by its ability to regulate histone methyltransferases or demethylases (Wang et al. 2017).

In summary, it is unclear whether tetracyclines have one or several modes of action. Despite this question and considering the wide range of protective effects reported in different models of various brain diseases, MIN and DOX are considered potential therapeutic agents in the treatment of neurodegenerative disorders (Noble et al. 2009a, b; Yong et al. 2004).

Doxycycline and minocycline in Parkinson's disease

Tetracycline derivatives, which have slowly been recognized as a genre of drugs with pleiotropic properties, have become an alternative form of therapy in neurodegenerative disorders in which inflammation contributes to disease progression (Reglodi et al. 2015; Socias et al. 2018). Indeed, this class of drugs has been reported to exert unique effects on complex pathologies (Griffin et al. 2010). The literature contains 242 clinical trials of MIN and 262 clinical trials of DOX in many types of systemic diseases. In particular, these clinical trials involve patients and/or experimental models related to numerous neurological conditions, including schizophrenia, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, PD, and autism (Supplementary Table 1; Gordon et al. 2007; Kelly et al. 2015; Loeb et al. 2004; Molloy et al. 2013; Parashos et al. 2014; Pardo et al. 2013; Zhang et al. 2003). Here, we review the evidence for the protective actions of MIN and DOX in PD.

Minocycline

The neuroprotective effects of MIN in PD experimental models have been reported since 2001. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) models of PD, MIN prevents dopaminergic nigrostriatal neurodegeneration (Du et al. 2001; He et al. 2001; Wu et al. 2002). In addition, MIN decreases MPTP-mediated nitrotyrosine formation and inhibits MPTP-induced microglial activation, which prevents the production of microglia-derived proinflammatory factors, including IL-1β, ROS, and NO (Wu et al. 2002). It also inhibits MPP + mediated iNOS expression in vivo and potently blocks NO-induced neurotoxicity in vitro (Du et al. 2001).

The neuroprotective effects of MIN have also been observed after chronic rotenone toxicity in wild-type rodents (Radad et al. 2010), parkin null mice (Casarejos et al. 2006), and PD model *Drosophila* (Faust et al. 2009). In addition, MIN administration has been shown to reduce the number of apomorphine-induced rotations in 6-hydroxydopamine (6-OHDA)-lesioned rats, the loss of tyrosine hydroxylase-positive cells, increasing the size and fiber density of the remaining nigral cells (Quintero et al. 2006). Moreover, MIN exhibits protective effects on nigrostriatal dopaminergic neurodegeneration in the *Weaver* mouse, which has a mutation in the gene encoding for the G-protein-activated inward rectifier potassium channel 2 (Peng et al. 2006).

To investigate the effects of anti-inflammatory treatments on regeneration, Worlitzer et al. (2013) administered MIN for 14 weeks starting 2–3 weeks after injections of 6-OHDA in a mouse model of PD. MIN treatment induced functional regeneration that was dopaminergic neuron activity-dependent. Anti-inflammatory treatment after the degeneration of dopaminergic neurons in the substantia nigra increased the activity of adult neural stem cells in the subventricular zone, which resulted in the generation of neuroblasts that migrated deeply into the lesioned striatum. These newly generated cells differentiated into mature striatal oligodendrocytes. These results suggested that oligodendrogenesis was responsible, at least in part, for the behavioral improvements in the PD symptoms due to the increased stability and efficiency of axonal function in the remaining ipsilateral and/or crossing contralateral dopaminergic neurons (Worlitzer et al. 2013).

Interestingly, MIN prevents *N*-methyl D-aspartate (NMDA) glutamate receptor-induced neuronal death by inhibiting the activation and proliferation of microglia cells in culture (Tikka and Koistinaho 2001). Those authors also showed that MIN inhibits the NMDA-induced activation of p38 MAPK and a specific p38 MAPK inhibitor, while not that of a p44/42 MAPK inhibitor, in microglial cells, which then reduces NMDA toxicity.

Nonetheless, conflicting evidence for the efficacy of MIN has been reported in animal models of PD (Sriram et al. 2006; Yang et al. 2003). MIN has variable and even harmful effects in MPTP models due to the exacerbation of the MPTP-induced damage to dopaminergic neurons both in vitro and in vivo (Yang et al. 2003). Additional uncertainty results from the apparent lack of robust therapeutic efficacy of MIN in clinical trials in which MIN-treated patients with PD exhibited trends for worse Unified Parkinson's Disease Rating Scale scores compared to placebo-treated controls (Gordon et al. 2007). In contrast, another trial showed additive neuroprotective effects of MIN when it was combined with creatine, which has been shown to reduce PD progression in patients (NINDS NET-PD, 2006). Thus, several questions on the efficacy of MIN as a viable PD treatment remain.

Doxycycline

DOX is a highly effective and inexpensive antibiotic with a broad therapeutic spectrum and exceptional bioavailability.

Not surprisingly, DOX is included in the World Health Organization's List of Essential Medicines needed for basic health care systems (http://www.who.int/medicines/publications/essentialmedicines/en/; Perez-Trallero and Iglesias 2003). DOX was immediately popular after its use was approved by the Food and Drug Administration in 1967 because of its simplified once (or twice)-a-day dosage regimen compared to the four-times-a-day dosing schedule of tetracycline. In addition, DOX presents minimal side effects, even after its long-term administration (Gompels et al. 2006; Langevitz et al. 1992; Smith et al. 2011).

DOX has various effects on central nervous system functions. Because it is already clinically available, it is an obvious and attractive candidate for drug repurposing. Subantimicrobial doses of DOX (20 mg twice daily with serum concentrations in the range of 200–600 ng/mL) have been repeatedly demonstrated as safe with no evidence of post-treatment microbiologic resistance (Payne et al. 2011).

The neuroprotective effects of DOX on dopaminergic neurons have been demonstrated both in vitro and in vivo (Cho et al. 2011; Lazzarini et al. 2013). These effects seem to result from antiapoptotic and anti-inflammatory mechanisms involving the downregulation of MMPs (Cho et al. 2011; Fig. 2). Nevertheless, it has become clear that the use of DOX to control Tet-ON/Tet-OFF systems (DOX-inducible systems) involves risk (Lewandoski 2001) in that the use of DOX per se produces unexpected experimental outcomes. Recently, we showed that the systemic treatment of mice in a 6-OHDA model of PD with DOX protected dopaminergic neurons (Lazzarini et al. 2013) and that this neuroprotection was associated with a reduction in microglial activation. This important discovery happened by accident (serendipity) when 6-OHDA-lesioned mice were fed chow containing DOX. Comparable results were obtained in another group of mice that were later administered DOX subcutaneously (Fig. 2). The 6-OHDA model causes neuroinflammatory responses (Taylor 2013; Tufekci et al. 2012), including reactive astrocytosis (Wachter et al. 2010) and microglial activation (Lazzarini et al. 2013; Marinova-Mutafchieva et al. 2009; Fig. 2). These experimental results strongly suggest that DOX is a promising alternative for the treatment of PD.

Additionally, our group has also reported a direct effect of DOX in the activation of primary microglia in vitro (Santa-Cecília et al. 2016). DOX reduces the LPS-induced activation of microglial cells in a concentration-dependent manner (200–300 μM) by preventing increase in the expression of Iba-1. Additionally, DOX reduces the expression of inflammatory mediators, such as TNF-α, ROS, and iNOS. This effect was associated with the inhibition of the production of the proinflammatory cytokines TNF-α and IL-1β by LPS. One possible molecular mechanism underlying these effects is that DOX inhibits the activation of the p38 MAPK and NF-κB signaling pathways

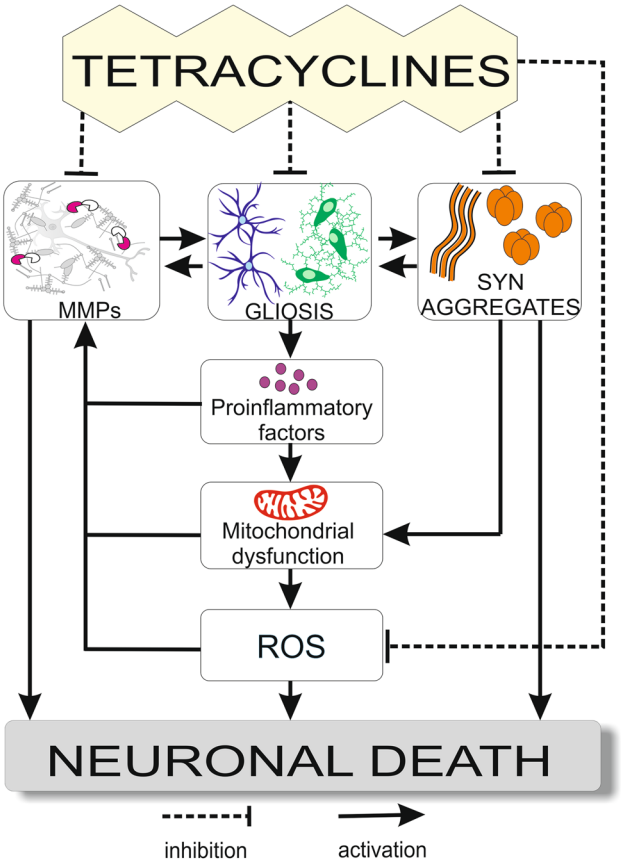


Fig. 2 Tetracycline and neuronal cell death. Tetracyclines can protect against neuronal cell death by directly suppressing expression of MMPs and activation of glial cells, remodeling α-synuclein early aggregates and scavenging ROS. Indirectly, DOX is able to inhibit mitochondrial dysfunction and subsequent oxidative damage caused by α-synuclein aggregates or production of proinflammatory mediators from glial cell activation, which, in turn, leads to MMP activation. *MMP* matrix metalloproteinase, *ROS* reactive oxygen species, *SYN* α-synuclein

in LPS-stimulated microglial cells. Similarly, Zhang et al. (2015) have thoroughly demonstrated that the effects of DOX in a rat model of PD occur through the inhibition of the LPS-induced degeneration of dopaminergic neurons by the downregulation of the expression of microglial major histocompatibility complex II.

Neuroinflammation and α-synuclein pathology interact synergistically and lead to PD neurodegeneration (Gao and Hong 2008). Neuron-associated proteins, particularly α-synuclein, are modified by oxidation to form nitrated α-synuclein, which misfolds and aggregates to create intracellular inclusions called Lewy bodies (Kosloski et al. 2010). More recently, González-Lizárraga et al. (2017) have reported that DOX reshapes α-synuclein oligomers and inhibits α-synuclein aggregation and the seeding of new oligomers, thus preventing cytotoxicity in dopaminergic cell lines.

DOX is clearly promising for preventing and inhibiting dopaminergic cell loss (Sapadin and Fleischmajer 2006) through its anti-inflammatory effects (Joshi and Miller 1997). Importantly, the long-term administration (up to 2 years) of subantimicrobial doses of DOX has not produced antibiotic side effects in clinical trials (Golub et al. 2016; Keijmel et al. 2017). Thus, subantimicrobial doses of DOX may represent a game changer in PD therapy that will benefit a considerable number of patients.

The feasibility of treatment with tetracycline, minocycline, and doxycycline in neurodegenerative diseases

The most common side effects of an antibiotic concentration (200 mg/day) of tetracycline is gastrointestinal upset (Carter 2003), increased photosensitivity, teeth discoloration, and bone formation and growth interference in children under the age of eight (Archer and Archer 2002; Gupta et al. 2006). Other common side effects of this antibiotic dose include nausea, vertigo, and mild dizziness, which are completely reversible upon discontinuation of the drug. Additionally, liver toxicity, pigmentation, and a lupus erythematosus-like syndrome may appear during the use of this drug (Garner et al. 2003).

Although tetracycline has been studied extensively, long-term studies are rare (Smith et al. 2005). Nonetheless clearly a major concern of the use of antibiotics as adjuncts to mechanical debridement procedures is the development of antibiotic side effects (Chopra and Roberts 2001). The administration of tetracyclyne antibiotic doses (200–400 mg/day) is responsible for the antimicrobial effects, which may result in bacterial resistance and alterations in endogenous flora. In contrast, clinical trials have demonstrated that the administration of subantibiotic doses (20–40 mg/day) does not alter bacterial susceptibility to antibiotics and results in anti-inflammatory effects (Payne et al. 2011; NINDS NET-PD Investigators 2006).

Studies on the neuroprotective effects of MIN in experimental models of neurodegeneration have had promising results. However, MIN has shown variable and even contradictory (beneficial and detrimental) effects in various species and models, which suggests an urgent need for the promotion of the publication of negative results (Diguet et al. 2004).

Accordingly, additional studies are required to determine the conditions required for the safe clinical administration of subantibiotic doses during the prolonged treatments necessary in the study of neurodegenerative diseases.

Conclusion and open questions

In this review, we presented the current experimental evidence for the potential use of tetracycline and its derivatives (MIN and DOX) as neuroprotective agents in PD. MIN and DOX, which are already clinically available, have protective actions with long half-lives, minor side effects, increased lipid solubilities, good tolerances, and excellent blood–brain barrier penetrations. The use of these drugs alone or in combination with other agents offers novel therapeutic approaches that target multiple pathways that lead to the degeneration of dopaminergic neurons in PD. Indeed, this class of drugs has been reported to exert unique effects on complex pathologies (Griffin et al. 2010). In brief, both are effective, and each exhibits unique pharmacological properties that may prove to be potentially advantageous.

Because the pathology of PD is very complex, the neuroprotective properties of MIN and DOX seem to be mediated by mechanisms other than their antimicrobial effects (Fig. 2): (1) the protection of dopaminergic cells through decreased levels of intracellular MMPs, which participate in cell death signaling; (2) prevention of the activation of microglia; (3) inhibition of the production of proinflammatory molecules; and 4) inhibition of the aggregation of α-synuclein, among others. These properties are not necessarily limited to MIN and DOX as other tetracyclines have also been shown to have beneficial effects on inflammation and apoptotic cell death.

In conclusion, tetracycline and its derivatives have been increasingly recognized for their anti-inflammatory and neuroprotective potentials. While the mechanisms underlying their benefits are still unclear, this novel mode of action of tetracyclines may help in the development of more specific and effective strategies in the treatment of neurodegenerative disorders. Finally, drug repurposing has potential for quickly bringing medications with known safety profiles to new patient populations.

Neuroprotective antibiotics are a potential treatment for chronic neurological disorders that have few existing treatments. DOX, which is listed on the World Health Organization's list of essential medicines and which is already clinically available, should be considered an excellent candidate in the development of therapeutic strategies for PD.

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