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Tetracycline compounds with non-antimicrobial organ protective properties: Possible mechanisms of action

Michael O. Griffin[a], Guillermo Ceballos[c,b], Francisco J. Villarreal[b,*]

[a] Transitional Year Residency Program, Wheaton Franciscan Healthcare-St. Joseph, Milwaukee, WI, United States
[b] Department of Medicine, University of California, San Diego, United States
[c] Escuela Superior de Medicina, Instituto Politecnico Nacional, Mexico, DF, Mexico

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ABSTRACT

Tetracyclines were developed as a result of the screening of soil samples for antibiotics. The first[t] of these compounds, chlortetracycline, was introduced in 1947. Tetracyclines were found to be highly effective against various pathogens including rickettsiae, as well as both gram-positive and gram-negative bacteria, thus becoming the first class of broad-spectrum antibiotics. Many other interesting properties, unrelated to their antibiotic activity, have been identified for tetracyclines which have led to widely divergent experimental and clinical uses. For example, tetracyclines are also an effective anti-malarial drug. Minocycline, which can readily cross cell membranes, is known to be a potent anti-apoptotic agent. Another tetracycline, doxycycline is known to exert anti-protease activities. Doxycycline can inhibit matrix metalloproteinases which contribute to tissue destruction activities in diseases such as periodontitis. A large body of literature has provided additional evidence for the "beneficial" actions of tetracyclines, including their ability to act as reactive oxygen species scavengers and anti-inflammatory agents. This review provides a summary of tetracycline's multiple mechanisms of action as a means to understand their beneficial effects.

1. Classical uses of tetracyclines

The parent compound, chlortetracycline, was first isolated in 1947 [1]. Soon after, other natural tetracyclines have been isolated, including tetracycline (TC), for which the family of molecules is named. Two of the more common semi-synthetic tetracyclines used clinically as antibiotics are doxycycline (DOX) and minocycline (MIN). Due to its broad-spectrum antibiotic efficacy, DOX is indicated for the treatment of a variety of infections, including anthrax, Chlamydial infections, community-acquired pneumonia, Lyme disease, cholera, syphilis, Yersinia pestis (plague), periodontal infections, and others. MIN also displays broad-spectrum efficacy and is most often used clinically in the treatment of severe acne, but it is also indicated for many of the same infections as DOX [2].

The tetracyclines exert their antibiotic effect primarily by binding to the bacterial ribosome and halting protein synthesis [3]. Bacterial ribosomes have a high-affinity binding site located on the 30S subunit as well as multiple low-affinity sites on both the 30S and 50S subunits [4]. Upon binding to the ribosome, the tetracyclines allosterically inhibit binding of the amino acyl-tRNA at the acceptor site (A-site), and protein synthesis ceases [5]. The use of tetracyclines has declined in recent decades due to the emergence of resistant strains of bacteria (Fig. 1). Tetracyclines are also effective but slow-acting antimalarial drugs [6]. DOX impairs the expression of apicoplast genes. Apicoplast (non-photosynthetic major organelles found in cells of plants) are abnormal in the progeny of DOX-treated parasites.

2. Chemical properties

TC, DOX, and MIN are all composed of a four ring core to which are attached various side groups (Fig. 2). The dimethylamino group at the C4 carbon on the upper half of the molecule has been shown to be necessary for antimicrobial activity. 4-De-dimethylamino tetracyclines, also called chemically modified tetracyclines (CMTs), lack antimicrobial activity *in vivo* presumably due to the inability of the molecule to adapt a zwitterionic form necessary for activity [7]. However, CMTs do retain the ability to bind other nonmicrobial targets, such as matrix metalloproteinases (MMPs), facilitating their use in the treatment of other diseases [8]. The lower half of the molecule is critical for binding to both prokaryotic and eukaryotic targets, and interference with this region reduces or eliminates the effectiveness of the drug [9]. This region is relevant as the site for metal ion chelation. Binding of tetracyclines to proteins,

* Corresponding author at: UCSD School of Medicine, Department of Medicine, 9500 Gilman Dr. BSB4028, la Jolla, CA 92093-0613, United States.
Tel.: +1 858 534 3630; fax: +1 858 534 0522.
E-mail address: fvillarr@ucsd.edu (F.J. Villarreal).

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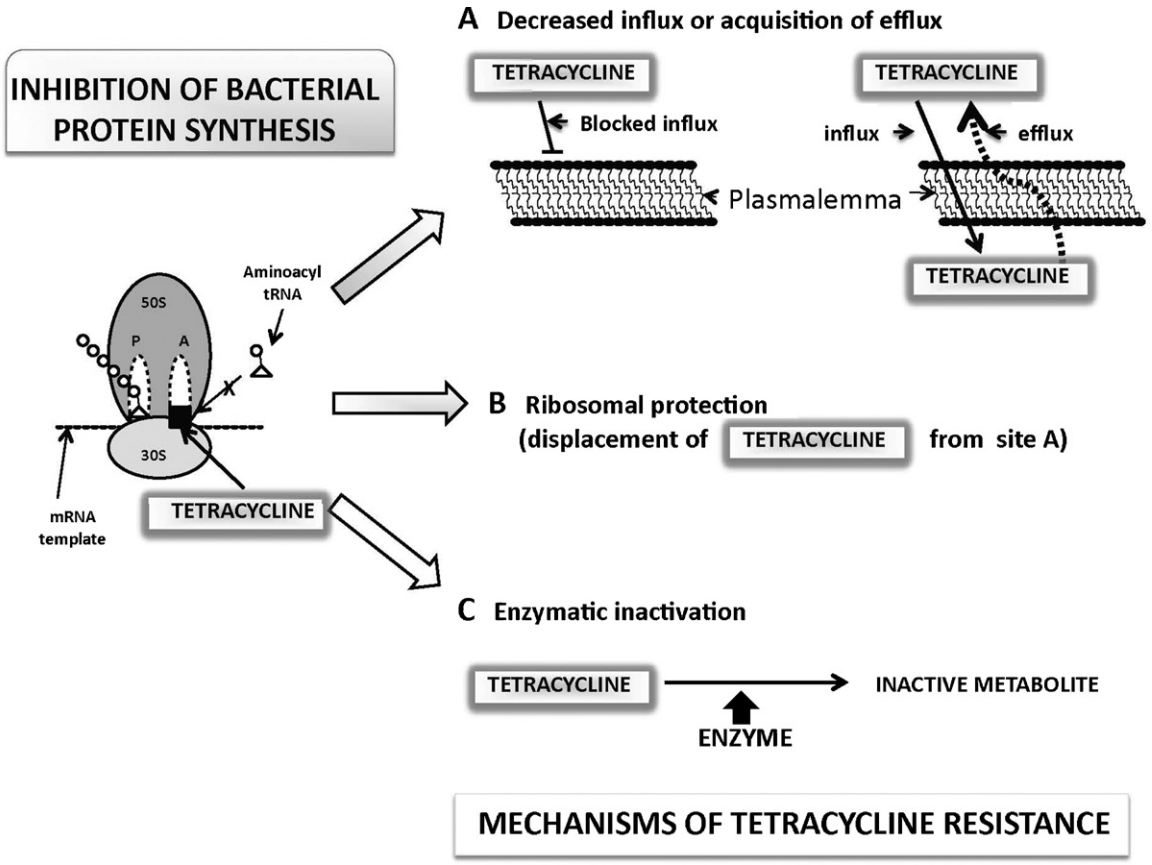

Fig. 1. Proposed means by which tetracyclines loose their protein synthesis inhibitory capacity in pathogens. This may occur secondary to the enhanced extrusion of the drug, decreased entry, displacement from ribosomes or enzymatic inactivation.

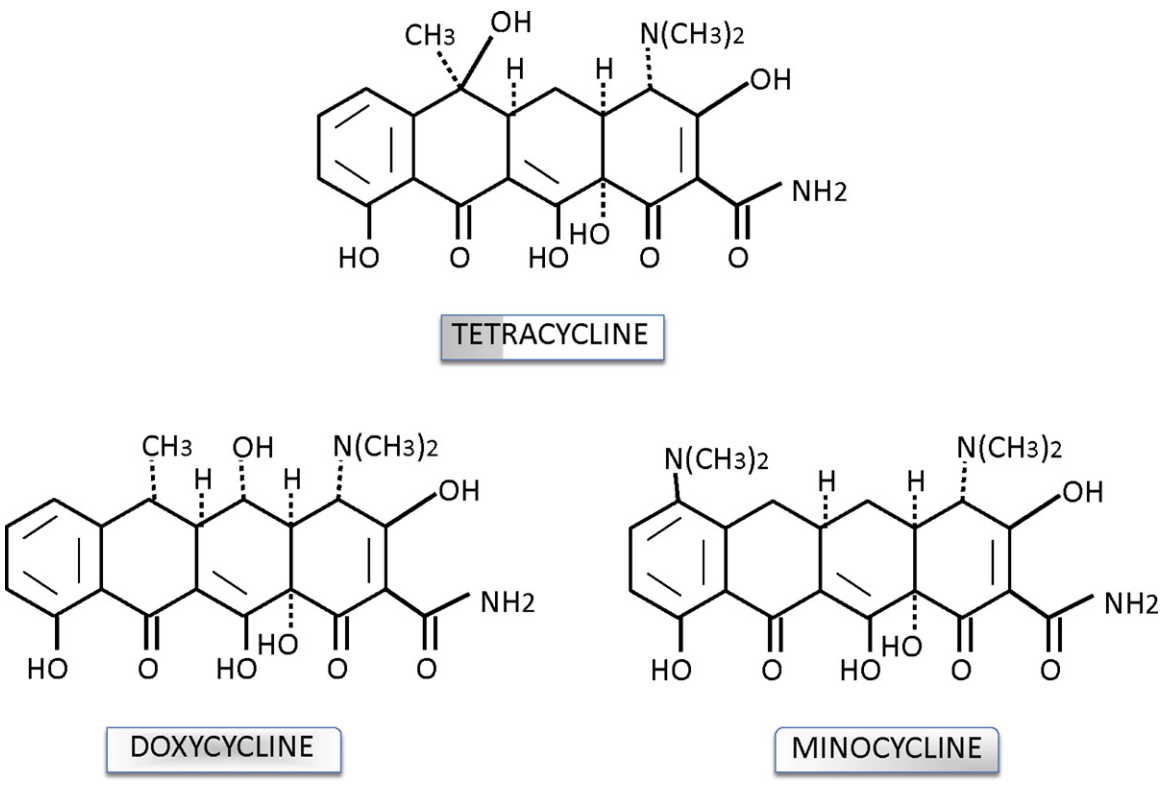

Fig. 2. Chemical structure of tetracyclines.

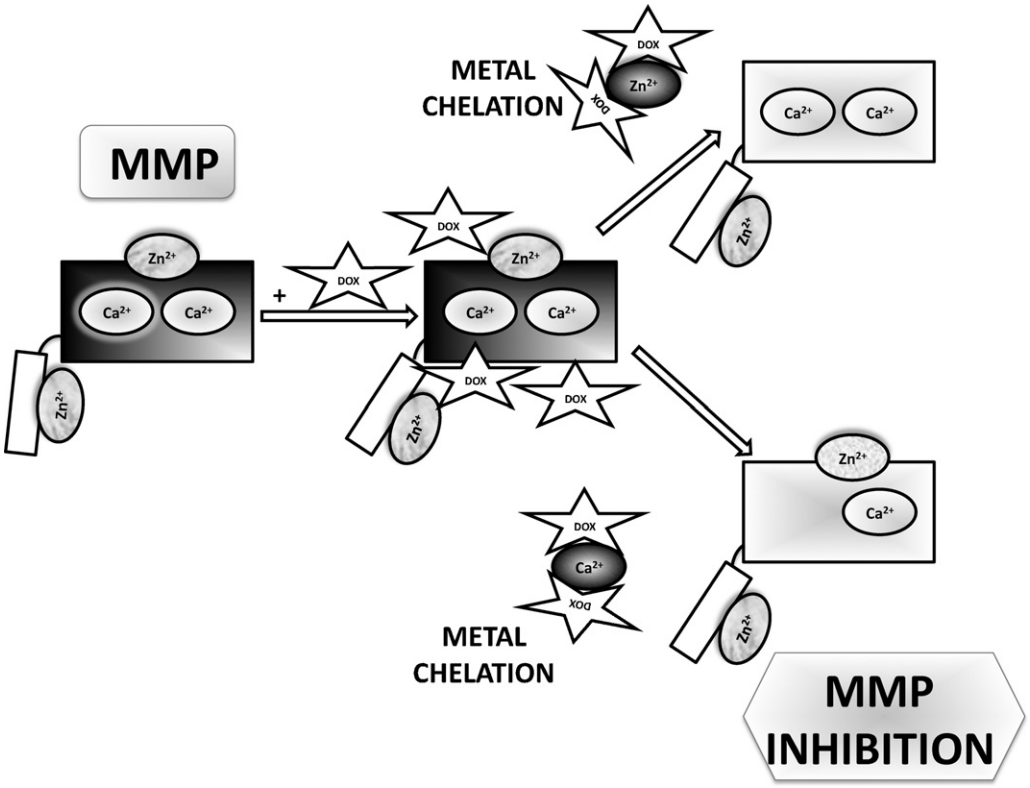

Fig. 3. Proposed means by which doxycycline acting through zinc and calcium chelation may act to inhibit matrix metalloproteinases.

including TetR, may be greatly enhanced when the tetracycline is complexed with divalent metal ions such as Ca^{2+} or Mg^{2+} [10]. The binding of tetracyclines to MMPs is thought to be mediated by the chelation of structural and catalytic Zn^{2+} ions within the enzyme (Fig. 3) [9,11]. In addition, binding to the bacterial ribosome involves binding to RNA-bound Mg^{2+} [12]. The strength of tetracycline–metal interaction is dependent on both the tetracycline and the metal ion present. In general, the affinity of the tetracyclines for different divalent metals is, in order of decreasing affinity: $Cu^{2+} > Co^{2+} = Fe^{2+} > Zn^{2+} > Mn^{2+} > Mg^{2+} > Ca^{2+}$ [13]. The affinities also differ and are highly dependent on pH and the presence of other metal ions [14–16]. The relative superiority of DOX as an MMP inhibitor is due to its increased affinity for Zn^{2+} compared with TC or MIN [7]. Other factors can also alter tetracycline activity; in general, there is a direct relationship between lipophilicity and activity against gram-positive bacteria. The lipophilicity of TC, DOX, and MIN, as determined by partitioning between octanol and aqueous buffer, are 0.025, 0.600, and 1.1, respectively [17], and the minimum inhibitory concentration against *Staphylococcus aureus* is 0.21, 0.19, and 0.10 μg/ml, respectively [18]. Lipophilicity also affects tissue distribution. MIN is able to cross the blood–brain barrier much more readily than DOX or TC. MIN attains levels in the brain nearly 3-fold higher than DOX, and TC is undetectable in the brain [19].

3. Matrix metalloproteinase (MMP) inhibition by tetracyclines

Probably the best characterized non-antimicrobial property of the tetracyclines is their ability to inhibit members of the MMP family of endopeptidases [20]. MMPs can be subdivided based on crude substrate specificities into the collagenases, gelatinases, stromelysins, and membrane-type MMPs (MT-MMPs) [21]. The collagenase group includes MMP-1, MMP-8, and MMP-13, which all cleave fibrillar collagens (types I and III). Collagen fragments subsequently denature into gelatins. The gelatinases, which include MMP-2 and MMP-9, proteolyze the gelatins. The gelatinases also degrade basement membrane collagen (type IV). The stromelysins includes MMP-3, MMP-7, MMP-10, and MMP-11 and are capable of degrading proteoglycans, laminin, fibronectin, collagen IV, and others. The cell membrane anchored MT-MMP include six different MMPs, of which MT1-MMP is the best characterized [22].

Inhibition of MMPs is beneficial in many pathological conditions in which MMP-mediated proteolysis of the extracellular matrix (ECM) contributes to pathogenesis, such as heart remodeling, tumor invasion, and inflammation [21,23,24]. Currently, the only clinically available MMP inhibitor is DOX, and it is indicated only for the treatment of periodontitis [23,25].

The mechanism by which tetracyclines inhibit MMPs has not been completely elucidated. It is believed that they exert their anti-proteolytic effects by both direct inhibition of MMPs and by inhibiting their expression. Direct inhibition of MMPs appears to be mediated by an interaction between the tetracycline molecule and metal ions within the MMP; it appears that the mechanism of inhibition is dependent on chelation of structural metals rather than chelation of the active site Zn^{2+} [26]. The effectiveness of tetracycline inhibition against various MMPs depends on the tetracycline species, MMP species, and the pH. It has been shown that DOX is more potent than MIN or TC against collagenases purified from rabbit corneas, with IC_{50} values of 15 μM, 190 μM, and 350 μM, respectively, and this trend may be explained by the relatively high affinity of DOX and low affinity of TC for Zn^{2+} [7]. The IC_{50} values for DOX against the collagenases MMP-8, MMP-13, and MMP-1 are 1–10 μM, 5–30 μM, and >200 μM, respectively [27–29]; the reasons for the differences are not clear. The pH of the system also affects inhibition as evidenced by the ability of DOX to inhibit MMP-8 at pH >7.1 and inability to inhibit at pH <7.1 [30]. In addition to inhibiting MMPs directly, tetracyclines also inhibit MMP synthesis. DOX inhibited cytokine induced MMP-8 mRNA and protein accumulation in cultured rat synovial fibroblasts [31]. In cultured

human skin fibroblasts, TC inhibited interleukin-1 (IL-1) induced MMP-3 expression [32]. Since MMP transcription is induced by a host of pro-inflammatory cytokines and other growth factors, including IL-1, IL-6, tumor necrosis factor-alpha (TNF-α), epidermal growth factor and others [33], it is likely that these upstream signaling cascades leading to MMP expression are important targets of tetracyclines. An interesting consequence of MMP inhibition is the indirect inhibition of serine proteases. MMPs can inactivate serine protease inhibitors (SERPINs) [34,35], and MMP inhibition with DOX or CMTs preserves SERPINs thereby blocking serine protease activity [36–40].

4. Reactive oxygen species scavenging by tetracyclines

Another well-characterized non-antimicrobial property of the tetracyclines is their ability to scavenge reactive oxygen species (ROS). DOX, MIN, and TC all have a multiple-substituted phenol rings, similar to vitamin E. The phenol ring is key to the ROS-scavenging abilities of these compounds. The reaction of the phenol ring with a free radical generates a phenolic radical that becomes relatively stable and unreactive due to resonance stabilization and steric hindrance by the phenol ring side groups [41]. MIN directly scavenges ROS in several cell-free mixed-radical assays with a potency comparable to vitamin E [41]. Depending on the assay used, MIN had an IC_{50} of 3–40 μM and is 9–250 times more potent as scavenger than DOX and 200–300 times more potent than TC. The superior scavenging ability of MIN is likely due to the presence of the diethyamino group on the phenolic carbon (Fig. 4).

5. Anti-apoptotic effects of tetracyclines

The tetracyclines possess anti-apoptotic properties (Fig. 3). MIN and DOX increased the survival of hippocampal neurons following global brain ischemia in gerbils, and this protection was associated with reduced caspase-1 expression [42], MIN has been evaluated in several other models of neuronal injury and found to also be protective against Huntington's disease [43], traumatic brain injury [44], and Parkinson's disease [45]. A key event in the execution of the apoptotic cascade is the activation of caspases, a family of cysteine proteases. Neuroprotection by MIN has been associated with a reduction in caspase-1 and/or caspase-3 expression, suggesting MIN was protective by inhibiting the expression of key factors within the apoptotic cascade. In addition to inhibiting caspase expression, MIN has also been shown to inhibit caspase activity by blocking its activation. Zhu et al. demonstrated that MIN inhibits cytochrome c release and caspase-3 activation in mice with amyotrophic lateral sclerosis [46]. Using isolated mitochondria, they also showed that MIN inhibited mitochondrial swelling induced by Ca^{2+} and Bid (a pro-apoptopic cytoclasmic factor), as well as cytochrome c release, indicating that the mitochondria, and perhaps the mPTP (mitochondrial permeability transition pore) were direct targets of MIN [46].

6. Anti-inflammatory effects of tetracyclines

The beneficial effects of TCs are likely associated with their aggregate "beneficial" actions including inhibiting proinflamma-

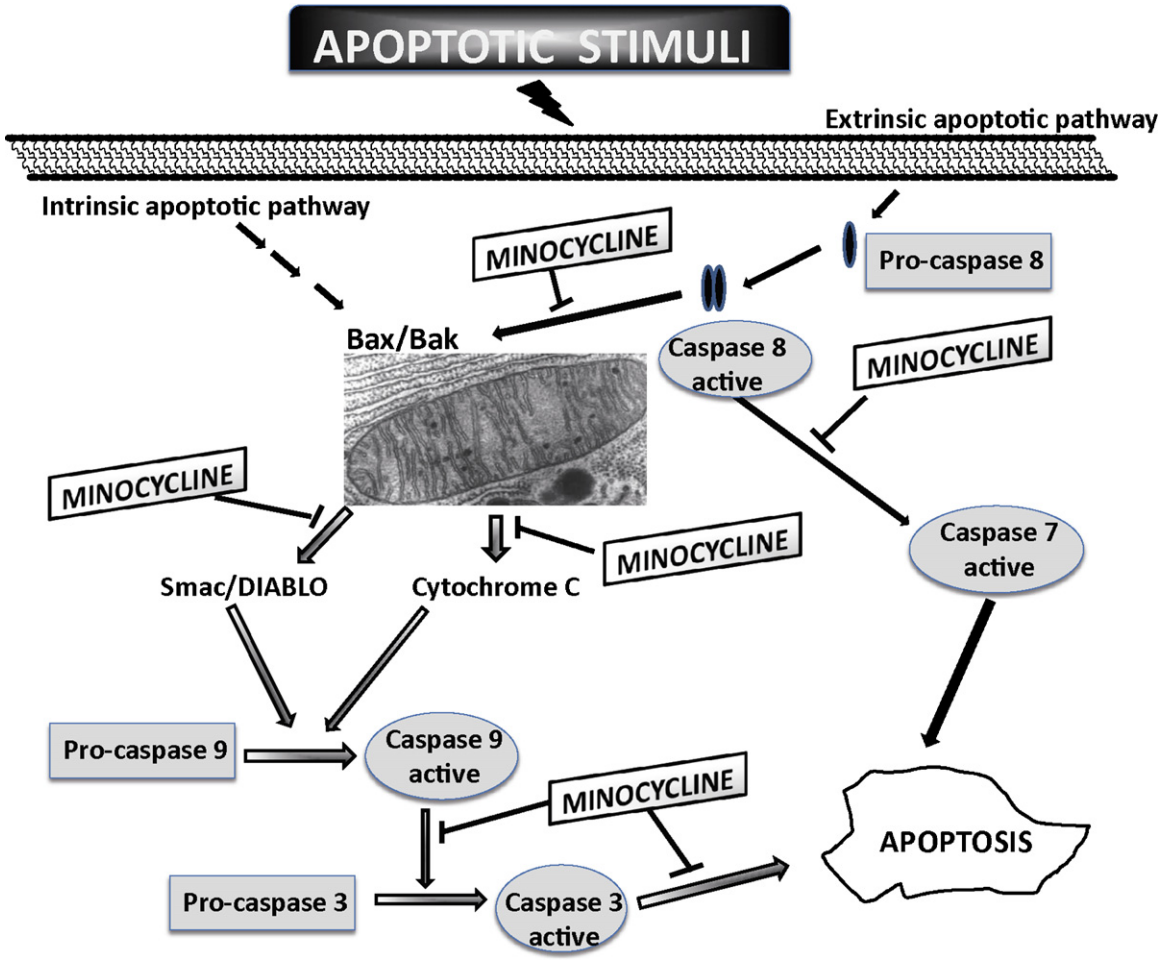

Fig. 4. Possible sites of action of minocycline on suppressing apoptotic signals in cells.

tory cytokine levels, MMPs and ROS. DOX is successfully used in the treatment of skin conditions such as acne and rosacea. Biopsies of inflammatory lesions of patients with acne yield increases in proinflammatory cytokines TNF-α and IL-1 [47]. These cytokines are known inducers of increases in MMP levels and of their activity. ROS and NO have also been described as playing a role in the pathophysiology of rosacea [48], NO likely mediates increases in vessel permeability and edema and may support erythema development.

Other actions add to the anti-inflammatory profile of TTCs. MIN and to a lesser extent DOX can inhibit phospolipase A_2 [49], can inhibit neutrophil migration [50], adherence [51] and the proliferation of lymphocytes [52]. These features aggregate as the anti-inflammatory profile of TCs.

7. Tetracycline uptake by tissues and cells

Tetracyclines have been reported to concentrate at the site of tissue injury. In the 1970s investigators using radiolabeled TC noted its capacity to accumulate in damaged myocardium and was used to diagnose infarcts [53,54]. Results demonstrated a correlation between infarct size, as determined by radiolabeled TC, and serum creatine kinase. The ability of TC to concentrate in other tissues is well known [55]. Dentists take advantage of the high concentration of DOX (Periostat®) in the inflammatory exudate in the periodontal lesion (gingival crevicular fluid) as a means to treat periodontitis. Gingival fibroblasts transport MIN in a concentration and temperature-dependent manner. At steady state, the cellular/extracellular concentration ratio was >60 for MIN. The uptake of tetracyclines also has been observed in neutrophils and may partly explain high levels observed in injured tissues [56]. Romero-Perez et al. explored the capacity of MIN to accumulate in myocardial tissue and cells [57]. MIN accumulated in myocardium several-fold greater than plasma levels. Accumulation was more pronounced in ischemic than normal myocardium. Cardiac fibroblasts and myocytes possess a comparable uptake system to that reported for gingival cells [58]. Their intracellular concentration could in theory reach millimolar levels. At these concentrations mass action effects are likely seen where the drugs may at the same time exert potent anti-oxidant, anti-MMP and other effects which in balance ultimately translate into cytoprotective effects.

8. Other potential uses of tetracyclines

This class of drugs have been reported as exerting unique effects on complex pathologies. In an experimental simian immunodeficiency virus (SIV) model of HIV central nervous system (CNS) disease, MIN reduced the severity of encephalitis, suppressed viral load in the brain, and decreased the expression of CNS inflammatory markers [59]. Tetracyclines also demonstrate protective effects on prion (PrP(Sc))-mediated brain damage. Animals injected intracerebrally with scrapie-infected brain showed a significant delay in the onset of clinical signs of disease and prolonged survival time with 1 mM TC before inoculation [60]. When TC was preincubated with highly diluted scrapie-infected inoculum, one-third of treated hamsters did not develop disease. Thus, tetracyclines appear to reduce prion infectivity through a direct interaction with PrP(Sc) and are potentially useful for inactivation of BSE- or vCJD-contaminated products and prevention strategies.

There are few agents as acutely damaging to tissues and living organisms as mustard gas. This alkylating agent causes massive blistering of the skin and severely damages the lungs by activating proteases (including elastases and MMPs) amongst other effects. In a study by Guignabert et al. guinea pigs were given mustard gas intratracheally [61]. A group of animals were pre-treated with DOX resulting in decreased gelatinase activity, decreased inflammation and notable decrease in histological lung epithelial lesions. Acute respiratory distress syndrome (ARDS) develops in the setting of diseases such as sepsis. With ARDS an infiltration of the lungs by neutrophils can lead to a massive activation of the cells yielding local tissue destruction and possibly the death of the subject. The destruction of lung tissue can be documented in bronchial lavage by the presence of protease such as elastases, MMP, collagen and elastin fragments. The emergence of new epidemics where ARDS may be an important cause of severe disease or death augments the spectrum of the possible use of tetracyclines to prevent or limit the development of respiratory system complications. Such is the case for H1N1 influenza and SARS (severe acute respiratory distress syndrome caused by a coronavirus). A potential scenario may be where there is high risk of exposure and contamination by a mutated version of a virus (such as in the case of the H1N1 influenza) by medical personnel where the use of tetracyclines may be justified as a means of preventing serious complications from developing upon exposure and infection.

CMTs (in particular COL-3) have also been examined for their anti-cancer therapeutic potential. MMP are involved in tumor metastasis and angiogenesis and are overexpressed in Kaposi's sarcoma (KS) cells. COL-3 when administered at 50 mg/day, demonstrated antitumor activity similar to other promising investigational KS drugs.

9. Conclusions

Tetracyclines have been recognized slowly over time as a genre of drugs with interesting pleiotropic properties. Their accumulation in injured tissues makes them almost appear to act as a smart drug. The recognition by scientists and clinicians of these collection of properties and of the safety profile of this class of drugs has led to the implementation of clinical trials to explore their possible beneficial effects in the setting of a wide variety of diseases. As CMT have proven to generate useful derivatives with unique properties, a rational modification of this class of drugs may lead to the development of novel compounds with greater therapeutic potential and safety profiles. Indeed, such creative efforts are currently the focus of various research groups ([49], add ref). However, it should be recognized that each member of the TTC family has both similar and more importantly, distinct properties from each other such as half-life and lipophilicity. Scientists when anticipating their use, need to make extensive considerations towards the desired "preferred" action (e.g. antiapoptotic vs antiprotease) and anticipated outcomes.

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