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Review article

A systematic review on potential mechanisms of minocycline in kidney diseases

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ABSTRACT

Kidney diseases need specialized health care and still are a reason of death. There is a large body of evidence that indicates minocycline possesses some cytoprotective effects beside of antibacterial properties. In this review, we aimed to explain cytoprotective mechanisms and kidney protection of minocycline. In order to find the effects of minocycline on kidney diseases a systematic literature search was performed, according to the guidelines proposed at the PRISMA statement in the electronic databases, including: PubMed, Scopus, and Web of Science up to August 2016, using the term 'minocycline' combined either by 'kidney' or 'renal' and published in English language. The following criteria were included: (1) studies that used minocycline in renal diseases; (2) full-text articles; (3) English language; (4) no limitation in publications with *in-vivo* or *in-vitro* and human or animal subjects. Our search provided a total of 1056 articles which 1045 of them were discarded due to not meeting the inclusion criteria. It has been clear that several factors, including apoptosis, oxidative stress, mitochondrial dysfunction and inflammation have pivotal roles in the development and progression of kidney diseases. Minocycline protective properties are *via* several ways, including anti-apoptotic, free radical scavenging, anti-inflammatory, effect on mitochondrial functions and inhibition of matrix metalloproteinase. This systematic review confirmed that minocycline could have significant effects on treatment of renal malfunctions. However, regarding any possible adverse effects of antibiotics, it appears that more investigation is still needed in this context.

Contents

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Introduction

Minocycline (7-dimethylamino-6-demethyl-6-deoxytetracycline) is a semi-synthetic broad-spectrum, clinically available as a bacteriostatic antibiotic belongs to the second-generation of tetracycline antibiotics family [1,2]. The history usage of tetracycline family came back from 1940s [3]. Because of both effectiveness and low adverse side effects, tetracyclines are extensively used for treatment of human and animal infections [4]. Its antibiotic action originates through binding to the bacterial 30S ribosome subunit in a reversible manner and does not allow to aminoacyl transfer RNA to enter the A site of the ribosome and then inhibits protein synthesis [5,6]. Compare to tetracycline, minocycline has a higher lipophilic solubility, permeability and almost completely gastrointestinal (GI) absorption leading to rapid access to circulation system and more access to target organs as well as easily crossing the blood-brain-barrier [7,8]. Elimination half-life of minocycline is varying from 11 to 27 h and main elimination ways are urine and stool [9,10]. There are a large body of evidence that indicate, minocycline has cytoprotective effects for attenuating or treatment of neurodegenerative diseases [11], epithelial ovarian cancer [12], ototoxicity [13], liver diseases [14], spinal cord injury [15], neuropathic pain [16], and kidney diseases [17]. As an anti-apoptotic agent, minocycline inhibits both extrinsic and intrinsic pathways of apoptosis [18]. Minocycline inhibits P38 mitogen activated protein kinases (MAPKs) which is importantly involved in microglia activation, inflammatory signaling, and apoptosis [19,20]. Minocycline inhibits apoptosis *via* up-regulation of Bcl-2, Bcl-xl, survivin, and Smac/Diablo as anti-apoptotic agents as well as down-regulation of Bax, Bid, Bak, XIAP, and Fas as pro-apoptotic proteins [21,22]. Furthermore, minocycline blocks opening of mitochondrial permeability transition pore (MPTP) and subsequently, release of apoptotic factors [23]. Minocycline inhibits apoptotic protease activator factor-1 (Apaf-1), which cleavage procaspase 9 to activated caspase 9 [24]. Moreover, minocycline inhibits caspase-3, -7, -8, -9 and -12 [25–28]. Minocycline can also prevent inflammation and cell death induced by DNA damage through inhibiting poly (ADP-ribose) polymerase-1 (PARP-1), an enzyme involved in repair of single-stranded DNA [29]. Anti-inflammatory effect of minocycline is due to modulating the activity of inflammatory cell chemotaxis and inflammatory cytokines. For instance, minocycline down-regulates pro-inflammatory cytokines, including tumor necrosis factor (TNF) alpha, interleukin-6 (IL-6), IL-1β, prostaglandin E2 (PGE2) production as well as phospholipase A2 (PLA2) and also up-regulates IL-10 as an anti-inflammatory cytokine [30–32]. Minocycline has a significant inhibitory effect on matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-2 (MMP-9) through both direct and indirect mechanisms. Direct inhibition mediated *via* interaction with metal ions within the enzyme and indirectly through down-regulation of MMPs [17]. Minocycline compared to doxycycline and tetracycline has 9–250 and 200–300 more times scavenging property respectively [33]. This high scavenging potency of minocycline is related to numerous phenol rings with multiple side groups, especially diethylamino group substituent [34]. Some studies reported minocycline properties on the mitochondrial respiratory chain. It is shown that minocycline does not modify complex IV activity, but inhibits complex II and III in concentration more than 100 μM [25]. Moreover, Garcia-Martinez et al. determined that minocycline inhibits complex I, III and IV in concentrations of 75–150 μM [35]. In this regards, it was reported that minocycline dose-dependently has the inhibitory effect on the respiratory chain at 150 μM [36]. Protective properties of minocycline have been reported in several studies on different pathological situations. In this regards, these questions will be emerging: Does minocycline have a protective effect on renal diseases? If it has, what is the role of minocycline for this effect? And what are the mechanisms for renal protection? In order to make a vision for minocycline effect on the renal pathological situation and answer to the above questions, in this systematic review, all studies and mechanisms of minocycline in renal diseases have been criticized.

Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [37].

Literature search

We performed a comprehensive search to identify all available studies in the electronic databases, including: PubMed, Scopus, and Web of Science up to August 2016, using the term 'minocycline' combined either by 'kidney' or 'renal'.

Inclusion criteria

Inclusion criteria included: (1) studies that used a combination of minocycline and kidney or renal diseases; (2) studies with full-text articles; (3) studies in English language; (4) without limitation in publications with *in-vivo* or *in-vitro* and human or animal subjects.

Exclusion criteria

Exclusion criteria included case report, editorials, and letter to the editor, not related abstracts, and review articles.

Data extraction

For each study, information including authors' names, type of renal diseases, modes, dosage and route of administration as well as outcomes was extracted independently. The extracted data and characteristics of the 13 included studies were summarized in Table 1.