

Antioxidant effect of doxycycline decreases MMP activity and blood pressure in SHR

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Abstract Increased matrix metalloproteinase (MMP) levels are involved in vascular remodeling of hypertension. In this study, we hypothesized that doxycycline (a MMP inhibitor) could exert antioxidant effects, reverse established vascular remodeling, and lower blood pressure in spontaneously hypertensive rats (SHR). SHR and Wistar-Kyoto rats received either doxycycline at 30 mg/kg/day by gavage or vehicle. Systolic blood pressure (SBP) was assessed weekly by tail cuff. After 5 weeks of treatment, morphologic changes in the aortic wall were studied in hematoxylin/eosin sections. MMP activity and expression were determined by in situ zymography using DQ gelatin and immunofluorescence for MMP-2. Dihydroethidium was used to evaluate aortic reactive oxygen species (ROS) production by fluorescence microscopy. Doxycycline reduced SBP by 25 mmHg. However, the antihypertensive effects were not associated with significant reversal of hypertension-induced vascular hypertrophy. SHR showed increased aortic MMP-2 levels which co-localized with higher aortic MMP activity and ROS levels, and all those biochemical alterations associated with hypertension were blunted by treatment with doxycycline. These results show

that MMP inhibition with doxycycline in SHR with established hypertension resulted in antioxidant effects, lower gelatinolytic activity, and antihypertensive effects which were not associated with reversal of hypertension-induced vascular remodeling.

Keywords Hypertension · SHR · Doxycycline · Oxidative stress · MMPs

Introduction

Hypertension is a major public health problem associated with increased risk of cardiovascular complications leading to high morbidity and mortality rates [1]. It is clear that chronic hypertension promotes cardiovascular remodeling, and this is a major mechanism leading to organ damage [2] and clinical events [3]. Therefore, while lowering blood pressure is of paramount importance [1], the use of other drugs that may help to reverse the cardiovascular remodeling of hypertension may be particularly useful in such patients [4].

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that degrade several components of the extracellular matrix and therefore play a key role in physiological and pathological remodeling [5]. Adding complexity to the biology of MMPs, growing evidence indicates that MMPs also degrade substrates that are not components of the extracellular matrix including drug receptors that affect cardiovascular responses [6, 7]. Importantly, increased vascular MMP activity has been shown in animal models of hypertension such as renovascular hypertension [8, 9], hypertension secondary to inhibition of endogenous nitric oxide synthesis (L-NAME model) [10], DOCA-salt [11], angiotensin II infusion [12], and in spontaneously

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