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The effect of sildenafil on rats with adenine—Induced chronic kidney disease

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ABSTRACT

The erectile dysfunction drug sildenafil has cardiopulmonary protective actions, and a nephroprotective action in cisplatin and ischemia-reperfusion–induced acute kidney injury. Here, we assessed its possible ameliorative action in a model of chronic kidney disease (CKD) using adenine feeding. Eight groups of rats were treated with saline (controls), adenine (0.25% w/w in feed daily for 5 weeks), and oral sildenafil (0.1, 0.5 or 2.5 mg/kg), either alone, or concomitantly with adenine. Urine was collected 24 h after the end of the treatments from all rats and blood pressure measured, followed by collection of blood and kidneys for the measurement of several functional, biochemical and histopathological parameters. Adenine treatment reduced body weight, creatinine renal clearance, and increased water intake and urine output, as well as the plasma concentrations of urea and creatinine, neutrophil gelatinase-associated lipocalin, and N-acetyl-β-D-glucosaminidase activity, and albumin in urine. Adenine also increased the concentrations of the uremic toxins indoxyl sulfate, uric acid and phosphate, and a number of proteins and inflammatory cytokines, and decreased that of several anti – oxidant indices. Renal histopathological markers of damage (inflammation and fibrosis) were significantly increased by adenine. Sildenafil, given simultaneously with adenine, induced a dose - dependent improvements in most of the above parameters, suggesting its possible use as adjunct treatment for CKD in humans.

1. Introduction

Chronic kidney disease (CKD) is a long – term condition that represents a major and growing public health problem in both developed and developing countries [1–4]. It is considered to be an important determinant of the poor health outcomes of major non-communicable diseases, which are rated as the main causes of death in the world [5]. It is estimated that 500 million people worldwide (1 in 10 adults) have some degree of CKD and almost half of people aged 75 or more have CKD [6,7]. CKD is associated with high prevalence of morbidity and mortality, especially due to cardiovascular dysfunction, and progression to end-stage renal disease (ESRD), imposing huge societal costs [8,9]. CKD is also known to cause significant gonadal dysfunction in both sex [10]. Till now there is no single drug to treat kidney function in CKD patients, and the current therapeutic approaches to slow down its progression are limited to normalization of insulin, glucose and blood pressure [11,12]. Therefore, the development of novel therapies (especially from drugs previously tested for other uses) to slow or reverse the deterioration in kidney function are highly needed.

The pathophysiological basis of CKD and its complications include inflammation, oxidative stress and apoptosis [13–15]. These pathophysiological changes are consistently seen in both humans and animals, and are major mediators of the disease, causing similar effects in different rodent CKD models [16,17]. Patients and laboratory animals with CKD have high plasma concentrations of inflammatory mediators (such as C-reactive protein, tumor necrosis factor and interleukin 1β) and several markers of nitro- and oxidative stress [13,18].

Animal models of CKD are useful in understanding the underlying biochemical, physiological and histopathological processes involving CKD and in developing and testing potential therapeutic agents.

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Table 1
Effect of treatment with sildenafil (S) on some physiological parameters in rats with adenine (A) – induced chronic kidney disease.

Parameters / Treatments	Control	A	S (0.1)	S (0.1) + A	S (0.5)	S (0.5) + A	S (2.5)	S (2.5) + A
Body weight change (%)	17.6 ± 0.8	−5.5 ± 0.8[a]	15.4 ± 1.8	−4.8 ± 1.2[a]	17.5 ± 1.4	−3.4 ± 0.7[a]	19.2 ± 2.4	−2.7 ± 0.4[a]
Relative kidney weight (%)	0.6 ± 0.0	1.7 ± 0.1[a]	0.6 ± 0.0	1.5 ± 0.1[a,b]	0.7 ± 0.0	1.3 ± 0.1[a,b]	0.7 ± 0.0	1.2 ± 0.0[a,b]
Water intake (mL)	23.9 ± 1.0	54.8 ± 5.0[a]	25.7 ± 4.2	48.3 ± 2.1[a]	13.2 ± 1.7	45.5 ± 3.0[a]	20.5 ± 0.9	41.2 ± 1.8[a,b]
Urine output (mL)	17.4 ± 1.1	45.5 ± 5.2[a]	11.8 ± 1.6	35.2 ± 1.7[a]	8.5 ± 1.4	30.2 ± 2.2[a,b]	9.0 ± 1.1	28.5 ± 0.9[a,b]
Feed intake (g)	16.3 ± 0.6	13.8 ± 2.5	17.5 ± 2.1	21.5 ± 1.7	12.1 ± 1.2	19.8 ± 1.4	15.1 ± 1.1	23.1 ± 2.1[b]
Feces out put (g)	8.1 ± 0.7	8.0 ± 0.6	9.3 ± 1.4	11.1 ± 1.2	7.3 ± 0.7	12.0 ± 1.0	6.9 ± 1.0	12.5 ± 0.9[a,b]

Values in the tables are mean ± SEM (number of rats per group is 6). Rats were treated with either A (0.25%w/w) in feed, or S (0.1, 0.5, 2.5mg/kg) orally during a treatment period of 35 days, either alone, or in combination. Different superscripts indicate significance as follows, where $P < 0.05$.
[a] denotes significance of Control group vs. different groups.
[b] denotes significance of A group vs. S + A treated groups.

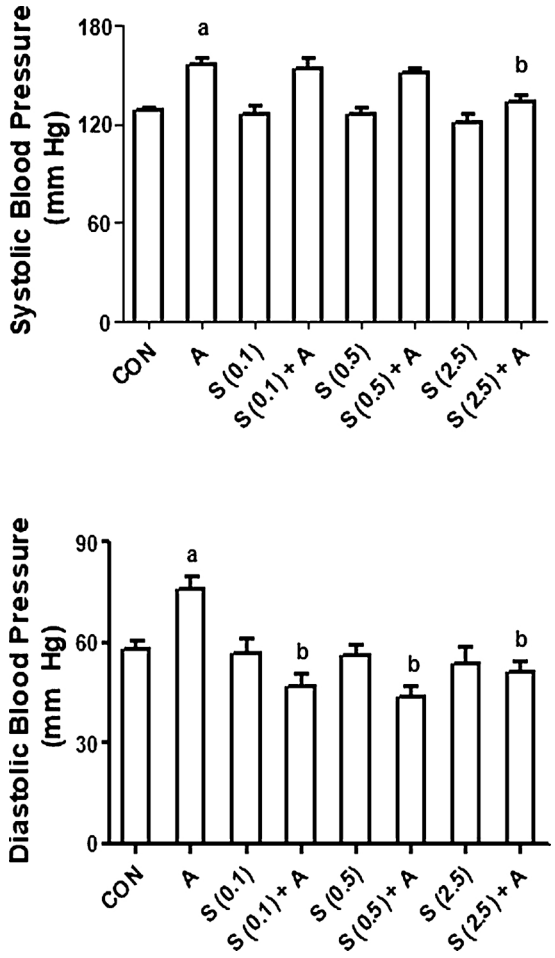

Fig. 1. Effect of sildenafil (S) treatment on the systolic and diastolic blood pressure in control rats (CON) and or rats treated, either singly or concomitantly, with adenine (A) or S, at doses of 0.1, 0.5 or 2.5 mg/kg. Each column and vertical bar represents mean ± SEM (number of rats per group is 6).
[a] denotes significance of control group versus different groups.
[b] denotes significance of adenine group versus adenine + sildenafil groups.

Adenine-induced model of CKD, first described by Yokozawa et al. in 1986, is one of the most successfully-adopted models. Adenine, giving in diet or solution, and its metabolites precipitate in the renal tubules causing their occlusion, ischemia and fibrosis leading to a progressive course of CKD and growth retardation which is more relevant to human CKD [19]. Furthermore, compared to 5/6 nephrectomy model of CKD, this model is easy to use, has low mortality rate, do not require surgical skills and follow a progressive nature similar to human CKD [20–22].

Sildenafil, a phosphodiesterase 5 (PDE-5) inhibitor, was developed initially for the treatment of angina pectoris, and was later repositioned to treat erectile dysfunction and pulmonary hypertension [23,24]. More recently it has been experimentally tried for treating other diseases that include prostate and colon cancer [25]. Sildenafil acts by increasing the concentration of cGMP in response to nitric oxide, and enhancing the relaxation of vascular smooth muscles. The expression and activity of PDE-5 is seen in various tissues including the kidneys [26]. Sildenafil is known to significantly decrease oxidative stress in brains of stressed mice and kidneys of rats with cisplatin or ischemia reperfusion injury-induced acute kidney injury and diabetic nephropathy [27–30]. The drug has also been shown to significantly ameliorate smoke-induced lung inflammation, and inflammatory demyelination in rats [31,32]. It has also been reported that sildenafil can prevent apoptosis of human first trimester trophoblast cells exposed to oxidative stress and decrease renal tubular apoptosis in rats and apoptosis in aged mice with beta amyloid load [33–35].

In view of the fact that sildenafil has anti-inflammatory, antioxidant and anti-apoptotic properties, it was thought of interest to see if it can mitigate the effects of adenine – induced CKD [36]. The effect of this drug was tested once before in a surgical model (5/6 nephrectomy) of CKD [37]. However, the present model (using adenine feeding) has been shown to be different in several aspects from the surgically - induced model of the disease [21].

2. Material and methods

2.1. Animals

Sprague – Dawley rats (9–10 weeks old, initially weighing about 250 g) were housed in a room at a temperature of 22 ± 2 °C, relative humidity of about 60%, with a 12 h light–dark cycle (lights on at 6:00 and off at 18.00), and fed ad libitum standard pellet chow diet containing 0·85% phosphorus, 1·12% calcium, 0·35% magnesium, 25·3% crude protein and 2·5 IU/g vitamin D3 (Oman Flour Mills, Muscat, Oman) and tap water. Ethical clearance was sought and obtained from Sultan Qaboos University (SQU) Animal Ethics Committee (Ethical Approval # SQU/AEC/2013-14/3), and all procedures involving animals and their care were carried out in accordance with international laws and policies (EEC Council directives 2010/63/EU, 22 September 2010 and NIH Guide for the Care and Use of Laboratory Animals, NIH Publications, 8th edition, 2011).