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Original article

Ameliorative potential of sitagliptin and/or resveratrol on experimentally-induced clear cell renal cell carcinoma

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ABSTRACT

The aim of this study was to assess the effect of sitagliptin with or without resveratrol on carcinogen-induced clear cell renal cell carcinoma. Sixty male Wistar rats were divided into 6 equal groups as follows: control; clear cell renal cell carcinoma group; clear cell renal cell carcinoma + sitagliptin group; clear cell renal cell carcinoma + resveratrol group; clear cell renal cell carcinoma + carboxymethyl cellulose group and clear cell renal cell carcinoma + sitagliptin + resveratrol group. Blood urea, serum creatinine, creatinine clearance, urinary N-acetyl beta-D-glucosaminidase (NAG), gamma glutamyl transpeptidase (GGT) and urinary albumin excretion rate (UAER) were determined. Renal tissue antioxidant enzymes, lactate dehydrogenase (LDH), nuclear factor (erythroid-derived 2)-like 2 (Nrf2), heme oxygenase-1 (HO-1), transforming growth factor beta-1 (TGF-β1), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and signal transducers and activators of transcription-3 (STAT3) were determined. Parts of the kidneys were subjected to histopathological and immunohistochemical examination for nuclear factor kappa B (p65). Sitagliptin and/or resveratrol induced significant improvement of the renal functions with significant increase in tissue antioxidant defenses and Nrf2/HO-1 content associated with significant decrease in tissue LDH, TGF-β1, TNF-α, IL-6 and STAT3 and alleviated the histopathological and immunohistochemical changes compared to the untreated clear cell renal cell carcinoma group. These effects were significant in sitagliptin/resveratrol combination group compared to the use of each of these drugs alone. In conclusion, sitagliptin/resveratrol combination might represent a beneficial therapeutic modality for amelioration of experimentally-induced clear cell renal cell carcinoma.

1. Introduction

Clear cell renal cell carcinoma is one of the renal cortical tumors characterized by malignant epithelial cells with clear cytoplasm and a compact-alveolar or acinar growth pattern [1]. It is characterized genetically by alterations of chromosome 3p. Recently, the incidence of clear cell renal cell carcinoma has been rising steadily in Europe and the United States for the past three decades. It is more likely to be symptomatic at presentation compared with other histological types of renal cell carcinoma [2]. Management of clear cell renal cell carcinoma usually depends on the stage of the tumor. Treatment for organ-confined clear cell renal cell carcinoma is primarily surgical through partial or radical nephrectomy depending on the size of the tumor. Cryoablation and radiofrequency ablation may be also tried for small localized tumors [3]. Patients with metastatic clear cell renal cell carcinoma may respond to cytokine immunotherapy with interleukin-2, although the median survival is not significantly increased [4]. Patients with clear cell renal cell carcinoma tend to have worse prognosis than patients with other histological subtypes of renal cell carcinoma. Recent trials are directed towards affecting the oxidative stress biomarkers, proinflammatory cytokines and other signaling pathways to improve the survival rate [5].

Sitagliptin is one of dipeptidyl peptidase-4 (DPP-4) inhibitors that were recently used for treatment of type 2 diabetes mellitus. Recent studies reported a role to DPP-4 inhibitors in cancer therapy, possibly due to their cytotoxic effects on tumor cells. Sitagliptin was reported to be more effective than vildagliptin in colon cancer cell lines [6]. Also, DPP-4 inhibitors were reported to suppress lung metastasis, possibly through down-regulation of autophagy resulting in increased apoptosis and modulation of the cell cycle [7]. These effects together with their antioxidant and anti-inflammatory properties may represent a new therapeutic modality for cancer therapy [8].

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Resveratrol is a phytoalexin agent that is commonly found in red wine and grape skins. Owing to the antioxidant and the anti-inflammatory properties of resveratrol, it was considered as a crucial agent for prevention of many cardiovascular disorders [9]. Recently, resveratrol was proven to act also as a chemopreventive agent against many types of tumors, possibly through affecting cell apoptosis, proliferation and inflammatory responses frequently encountered in cancer [10]. Moreover, resveratrol was reported to inhibit efflux transporters such as P-glycoprotein and multi-drug resistance-associated proteins which play a major role in resistance of cancer cells to the different chemotherapeutic agents [11]. The aim of this study was to assess the effect of sitagliptin with or without resveratrol on carcinogen-induced clear cell renal cell carcinoma.

2. Materials and methods

2.1. Drugs and chemicals

Sitagliptin was obtained in powder form from Wuhan Golden Wing Industry & Trade Co., Ltd., China. Resveratrol, ferric nitrate, sodium bicarbonate, disodium salt of nitrilo tetra acetic acid (NTA) and diethyl nitrosamine (DEN) were purchased from Sigma Aldrich Co., Saint Louis, Missouri, USA. Carboxymethyl cellulose (CMC) was obtained from ADWIC Co., Cairo, Egypt. Sitagliptin was dissolved in distilled water. Resveratrol was suspended in 0.3% CMC solution. Ferric nitrilo tetra acetic acid (Fe-NTA) solution was prepared immediately before its use by the method of Awai et al. [12] as modified by Athar and Iqbal [13]. Briefly, ferric nitrate (0.16 mmol/kg body weight) solution was mixed with four folds molar excess of disodium salt of NTA (0.64 nmol) and pH was adjusted to 7.4 with sodium bicarbonate solution. The concentration of the prepared Fe-NTA solution was 10 mL/kg body weight.

2.2. Experimental animals

In this study, we used sixty male Wistar rats weighing about 120–150 g. They were allowed to acclimatize for two weeks before starting the experiment. The animals were kept in a special room at a constant temperature of 24 ± 3 °C with relative humidity of 60 ± 10%, exposed to 12 h light/dark cycles with free access to food and tap water. This study was approved by the research ethics committee of faculty of pharmacy, Taif university with approval number REC/FOP-TU/224. All the experiments were conducted according to the national research council's guidelines. Animal handling was followed according to Helsinki declaration of animal ethics.

2.3. Induction of clear cell renal cell carcinoma

In all groups except the control group, clear cell renal cell carcinoma was induced by a single intraperitoneal injection of DEN in a dose of 200 mg/kg body weight. Ten days later, carcinogenesis was promoted by intraperitoneal injection of Fe-NTA in a dose of 9 mg Fe/kg body weight twice weekly for 24 weeks [14].

2.4. Experimental design

Rats were randomized into six equal groups (10 rats/group) as follows:

Group (1): Control untreated group.

Group (2): Carcinogen-induced clear cell renal cell carcinoma group [14].

Group (3): Received sitagliptin in a dose of 20 mg/kg body weight daily by oral gavage beginning immediately after starting administration of Fe-NTA for 24 weeks [15].

Group (4): Received resveratrol in a dose of 30 mg/kg body weight daily by oral gavage beginning immediately after starting administration of Fe-NTA for 24 weeks [16].

Group (5): Received 0.3% CMC solution daily by oral gavage beginning immediately after starting administration of Fe-NTA for 24 weeks.

Group (6): Received sitagliptin concomitantly with resveratrol in the above mentioned doses daily by oral gavage beginning immediately after starting administration of Fe-NTA for 24 weeks.

2.5. Assessment of the renal function tests

At the end of the experimental period, rats were kept in special metabolic cages for 24 h urine collection. Urine samples were centrifuged at 1400 rpm for 5 min after proper dilution and the supernatant was collected. Twenty-four hours urinary protein levels were measured according to the method of Fujita et al. [17]. The urinary albumin excretion rate (UAER) was measured using the following formula:

UAER (mg/24 h) = 24 h total volume of urine (L) × Urinary protein levels (mg/L)

Urinary N-acetyl beta-D-glucosaminidase (NAG) activity was determined according to Price [18]. Urinary gamma glutamyl transpeptidase (GGT) activity was assessed using the method of Szasz [19]. Then, rats were fasted overnight and anaesthetized with thiopental sodium (30 mg/kg body weight, intraperitoneal). Blood was collected from the retro-orbital plexus then prepared and used for assessment of blood urea according to Natelson et al. [20], serum and urinary creatinine according to Owen et al. [21] and creatinine clearance using the following formula [22]:

$$\text{Creatinine clearance(ml/min)} = \frac{\text{Urinary creatinine (mg/dl)} \times \text{24 hours urine volume(ml)}}{\text{Serum creatinine (mg/dl)} \times 1440}$$

Both kidneys were extracted, freed from blood and cleaned with ice cold saline. The right kidney was homogenized in 0.1 M Tris–HCl buffer of pH 7.4 at 4 °C in a potter homogenizer, at 600 rpm for 3 min. The filtrate was used for determination of the tissue biochemical parameters. The left kidney was used for histopathological and immunohistochemical examination.

2.6. Assessment of renal tissue oxidative stress parameters

The supernatant was used for assessment of tissue catalase (CAT) according to Sinha method [23], tissue superoxide dismutase (SOD) according to Marklund and Marklund [24], tissue glutathione peroxidase (GPx) according to Ellman's method [25] and tissue thiobarbituric acid derivatives (TBARS) according to Wright et al. [26].

2.7. Assessment of renal tissue nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and heme oxygenase-1 (HO-1) content

Tissue Nrf2 and HO-1 contents were measured using ELISA kits obtained from Cloud clone, Uscn Life Science, INC. USA, according to the manufacturer's instructions.

2.8. Assessment of renal tissue transforming growth factor beta 1 (TGF-β1), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and signal transducers and activators of transcription-3 (STAT3)

TGF-β1 was determined using kits supplied by Uscn Life Science Inc. Wuhan, according to the manufacturer's instructions. TNF-α was determined by using rat TNF-α ELISA kits of Ray Biotech, Inc. according to the manufacturer's instructions. IL-6 was measured using ELISA kits supplied by Sigma Aldrich Co. according to the instructions of the manufacturer. STAT3 levels were determined using ELISA kits supplied by RayBiotech, Inc., USA according to the manufacturer's instructions.

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