JOURNAL OF FUNCTIONAL FOODS 5 (2013) 316–326

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Dietary supplementation of flaxseed oil ameliorates the effect of cisplatin on rat kidney

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ARTICLE INFO

Article history:
Received 17 May 2012
Received in revised form
31 October 2012
Accepted 6 November 2012
Available online 6 December 2012

Keywords:
Carbohydrate metabolism
Cisplatin
Flaxseed oil
Nephrotoxicity
Oxidative stress

ABSTRACT

Cisplatin (CP) is an effective chemotherapeutic agent widely used in the treatment of many malignant tumours. However, its therapeutic utility is limited by dose dependent nephrotoxicity. Several agents/strategies have attempted to prevent CP nephrotoxicity but were not found suitable for clinical practice. Dietary flaxseed oil (FXO), a rich source of omega-3 fatty acids has been shown to prevent/reduce the progression of certain types of cardiovascular and renal disorders. The protective effect of FXO on CP induced nephrotoxic and other deleterious effects was investigated. Rats were prefed experimental diets for 10 days and then received a single dose of CP (6 mg/kg body weight) intraperitoneally while still on diet. Serum/urine parameters, enzymes of brush border membrane (BBM), oxidative stress and carbohydrate metabolism in rat kidney were analyzed. CP nephrotoxicity was recorded by increased serum creatinine and blood urea nitrogen. CP decreased the activities of metabolic enzymes, antioxidant defense system and BBM enzymes. In contrast, FXO alone increased enzyme activities of carbohydrate metabolism and brush border membrane. FXO feeding to CP treated rats markedly enhanced resistance to CP-elicited deleterious effects. Dietary FXO supplementation ameliorated CP induced specific metabolic alterations and oxidative damage due to its intrinsic biochemical antioxidant properties.

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1. Introduction

Cisplatin (cis-diamminedichloroplatinum II, CP) and other platinum derivatives are among the most effective chemotherapeutic agents against solid tumours, including ovarian, head and neck carcinomas and germ cell tumours. Dose dependent nephrotoxicity is the major limitation of this compound, sometimes requiring a reduction in dose or discontinuation of treatment (Schrier, 2002). Approximately 25–35% of patients develop evidence of nephrotoxicity following a single dose of cisplatin (Saad, Arafah, & Najjar, 2007). Cisplatin nephrotoxicity is chiefly characterized by tubular damage, primarily affecting the proximal tubules. Tubular damage may range from a mere loss of brush border of epithelial cells to an overt tubular necrosis in severe cases (Meyer & Madias, 1994). Mitochondria, lysosomes and microsomes are critical CP

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Abbreviations: ACPase, acid phosphatase; AKI, acute renal injury; ALP, alkaline phosphatase; BBM, brush border membrane; BBMV, brush border membrane vesicles; BUN, blood urea nitrogen; CP, cisplatin; CPFXO, cisplatin-flaxseed oil; FXO, flaxseed oil; FBPase, fructose-1,6-bisphosphatase; G6Pase, glucose-6-phosphatase; G6PDH, glucose-6-phosphate dehydrogenase; GGTase, γ-glutamyl transferase; GSH-Px, glutathione peroxidase; HK, hexokinase; LAP, leucine aminopeptidase; LDH, Lactate dehydrogenase; MDH, malate dehydrogenase; ME, malic enzyme; $NADP^+$, nicotinamide adenine dinucleotide phosphate; PUFA, poly unsaturated fatty acids; ROS, reactive oxygen species; Scr, serum creatinine; SOD, superoxide dismutas

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http://dx.doi.org/10.1016/j.jff.2012.11.002

targets (Leibbrandt, Grushenka, Metz, Ozobia, & Haskins, 1995; Zhang & Lindup, 1993). Functional alterations are characterized by change in urine volume, increase in blood urea nitrogen and serum creatinine (Dauggard, 1990).

Although the pathogenesis of cisplatin-induced acute renal injury (AKI) has been the focus of a large number of studies, the underlying mechanisms are not yet fully elucidated. Recent studies suggest that cisplatin nephrotoxicity is a complex and multifaceted process in which cisplatin triggers cellular responses involving multiple pathways that culminate in renal damage and necrosis (Pabla & Dong, 2008; Siddik, 2003). It has been suggested that CP induces renal damage by free radical generation, such as hydroxyl radical and superoxide radical anion, by altering arginine metabolism, by increasing activity of calcium independent nitric oxide synthase and more recently by apoptosis (Arany, Megyesi, Kaneto, Price, & Safirstein, 2004; Devipriya & Shyamala Devi, 1999; Santos et al., 2007). However, CP induced oxidative stress has been shown to be strongly involved in acute renal injury (Gonzales et al., 2005).

There is a continuous search for agents that provide nephroprotection against CP and other platinum drugs (Ali & Al Moundhri, 2006). These include antioxidants, modulators of nitric oxide, diuretics, and cytoprotective and apoptotic agents (Ali & Al Moundhri, 2006; Cetin et al., 2006; Conklin, 2004). However, none of these were found to be safe/suitable for clinical use in protecting against CP nephrotoxicity. The approach of identifying naturally occurring dietary sources and using them as cytoprotectants provides a strategy that is of great interest for CP chemotherapy. Nutritional recommendations have recently promoted the increased need to consume omega-3 (omega-3/n-3) polyunsaturated fatty acids (PUFAs) (Simopoulos, 1999). Flaxseed (*Linum usitatissimum*) is the richest dietary source of omega-3 fatty acids among plant sources. Flaxseed is widely used for its edible oil in many parts of the world. A number of investigations have demonstrated that diet supplemented with flaxseed oil has profound beneficial health effects in various pathologies (Chen, Stavro, & Thompson, 2002; Lin et al., 2002; Newairy & Abdou, 2009). The essential fatty acids specifically omega-3 fatty acids in flaxseed oil are considered as the key healing components (Larsson, Kumlin, Ingelman-Sundberg, & Wolk, 2004). The concentration of α-linolenic acid (omega-3 PUFA), a potent anticarcinogen (Williams et al., 2008) in flaxseed oil ranges from approximately 40–60%. Other bioactive constituents, such as linoleic acid and oleic acid are each present at 15% levels. Flaxseed is also the richest source of lignans, which have been reported to have antioxidant and hypolipidemic effects (Newairy & Abdou, 2009; Shahidi, 2000). Inclusion of flaxseed in the diet in animal studies has shown that it can inhibit arrhythmogenesis during ischemia–reperfusion (Ander, Weber, Rampersad, & Gilchrist, 2004), inhibit atherogenesis (Prasad, 2000, 2005) and protect during hypercholesterolemic conditions (Dupasquier, Weber, Ander, & Rampersad, 2006). Dietary supplementation of flaxseed was shown to inhibit the growth and development of prostate cancer in the transgenic adenocarcinoma mouse prostate model (Lin et al., 2002). Flaxseed has also been reported to inhibit human breast cancer growth and metastasis and down-regulate expression of insulin-like growth factor and epidermal growth receptor (Chen et al., 2002). Earlier studies have shown that flaxseed oil prevents lead induced neuro- and nephrotoxicity (Abdel-Moniem, Dkhil, & Al-Quraishy, 2010, 2011). We have recently reported that FXO mitigates CP induced hepatotoxic effects (Naqshbandi, Wasim, Sana, & Khan, 2012). However, the renoprotective potential of FXO in CP nephropathy has not yet been explored.

Considering the potential clinical use of CP and numerous health benefits of FXO, the present work was undertaken to study the biochemical events/mechanisms of CP nephropathy and its protection by dietary FXO. We hypothesized that flaxseed oil would prevent CP-induced nephrotoxicity due to its intrinsic biochemical and antioxidant properties that would lead to improved metabolism and antioxidant defense mechanism of the kidney. The results obtained indicate that dietary supplementation with flaxseed oil markedly ameliorate CP induced nephrotoxicity parameters and support a potential therapeutic use of CP + FXO combination in combating cancer without nephrotoxic and other harmful side effects.

2. Materials and methods

2.1. Chemicals and drugs

Flaxseed oil: Omega Nutrition Canada Inc. (Vancouver, BC, Canada), Cisplatin (Sigma–Aldrich Chemical Corp., St. Louis, MO, USA). All other chemicals used were of analytical grade and were purchased either from Sigma Chemical Corp. or SRL (Mumbai, India).

2.2. Diet

A nutritionally adequate laboratory pellet diet was obtained from Aashirwaad Industries, Chandigarh (1544, Sector 38-B, Chandigarh, India). Normal diet (ND) was prepared by crushing the pellets finely and adding vitamin E as DL-α-tocopherol (270 mg/kg chow) to the crushed diet. Flaxseed oil (FXO) diet was prepared by adding 15% flaxseed oil in diet by weight to the normal diet. The diet was stored in airtight containers. Vitamin E was added in order to meet the increased metabolic requirement for antioxidants on a diet high in polyunsaturated fatty acids.

2.3. Experimental design

The animal experiments were conducted according to the guidelines of Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India. Adult male Wistar rats (10–12 rats/group) weighing between 150 and 200 g were used in the study. Animals were acclimatized to the animal facility for a week on standard rat chow and allowed water ad libitum under controlled conditions of 25 ± 2 °C temperature, 50 ± 15% relative humidity and normal photoperiod (12 h dark and light). Four groups of rats entered the study after acclimatization. They were fed on either normal diet (control and CP groups) or FXO diet (CPFXO and FXO groups). After 10 days, rats in the two groups (CP and CPFXO) were administered a single dose of CP intraperitoneally

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