CINNAMON EXTRACT REGULATES GENE EXPRESSION OF LIPID AND CARBOHYDRATE METABOLISM IN STREPTOZOTOCIN INDUCED DIABETIC WISTAR RATS

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ABSTRACT

Cinnamon is a herbal medication plant used widely for many diseases in the Middle East and ancient countries. Cinnamon Extract (CE) contains many active substances that modulate insulin sensitivity and acts as anti-diabetic medication. Diabetes mellitus is a disease characterized by disturbance in carbohydrate and lipid metabolism. The aim of this study was to examine the effect of Cinnamon Extract (CE, 200 mg kg\(^{-1}\) body weight) on genes expression of lipid and carbohydrate metabolism in Streptozotocin (STZ) induced diabetes in Wistar rats. Administration of CE to STZ diabetic rats for 2 months normalized TG, cholesterol, VLDL, HDL and glucose levels. CE administration increased FAS and STREB-1c gene expressions that were inhibited in diabetic rats. Moreover, CE inhibited significantly the increase in LPL, HSL and resistin expression. In parallel, CE increased the expression of PPECK and GLUT2 and inhibited the decrement in IGF and PK expression. In conclusion, CE regulates the expression of genes related to lipid and carbohydrate metabolism in a way to control the metabolic disorders occur during diabetes.

Keywords: Cinnamon, Diabetes, Carbohydrates, Lipids, Metabolism

1. INTRODUCTION

Diabetes is a chronic metabolic disease occurred due to either destruction of \(\beta\) cells of pancreas or insulin resistance occurred during obesity and its related metabolic disorders (Hall, 2003; Havel, 2004). Diabetes is associated with an increased risk of coronary heart disease, stroke, hypertension, renal failure, type 2 diabetes, dyslipidemia and all cause mortality (Trayhurn and Beattie, 2001). Clinically diabetic patients characterized by marked increase in blood glucose levels followed by mild hyperlipidemia (Reddy \textit{et al.}, 2009). Traditional herbal medicine has been widely used for diabetes treatment and is recognized as an interesting alternative to conventional medicine (Kameswara-Rao \textit{et al.}, 1997) especially in the third world countries and therefore represent new avenues in the search for alternative hypoglycemic drugs (Day, 1998). Diabetes treatment depends mainly on regulation of genes related to glucose and/or carbohydrate metabolism. Glucose transport is the rate limiting step in carbohydrate metabolism (Maughana, 2009) which is facilitated by Glucose Transporters (GLUT) across the cell membrane (Anand \textit{et al.}, 2010).
So, drugs facilitate GLUT4 translocation and improve insulin sensitivity together with carbohydrate and lipid metabolism could be beneficial for the treatment of diabetes (Kipmen-Korgun et al., 2009; Shepherd and Kahn, 1999). Usage of natural products as cinnamon and other dietary modulators with anti-diabetic activity are the first choice of diabetic patients. This tendency is because insulin, to date, cannot be used orally and its repeated injections have many undesirable adverse effects. In addition, most of hypoglycemic agents or drugs are not effective to decrease blood glucose levels in chronic diabetic patients (Cheng and Fantus, 2005).

Cinnamon contains active components as cinnamic aldehyde, cinnamic acid, tannin and methyl hydroxychalcone polymer with insulin-mimetic properties (Kim et al., 2006). CE has hypoglycemic and hypolipidemic effect in rats (Qin et al., 2003) and increases insulin sensitivity and glucose uptake in adipocytes (Khan et al., 2003; Jarvull-Taylor et al., 2001; Yaghmoor and Khoja, 2010). The mechanism of hypoglycemic effect of CE are reported in vitro and in vivo studies through enhancement of glucose uptake by activating insulin receptor kinase activity, autophosphorylation of insulin receptor and glycogen synthase activity (Kannappan et al., 2006). CE reduces lipid profiles in fructose-fed rats and affects immune responses by regulating anti-, proinflammatory and glucose transporter gene expressions in mouse macrophages (Cao et al., 2008) but CE effects on genes of carbohydrate and lipids have not been examined yet. Cinnamon has a hepatoprotective effect against carbon tetrachloride induced oxidative stress and liver injury in rats (Moselhy and Ali, 2009). Clinical and animal studies have confirmed a strong relationship between obesity and hypertension with diabetes (Mohamed-Ali et al., 1998). During diabetes there is alteration in lipid and carbohydrate metabolism. As lipolysis, glycolysis and gluconeogenesis enhanced to overcome metabolic needs. Those processes are regulated by variable enzymes as Lipoprotein Lipase (LPL), Hormone Sensitive Lipase (HSL), Fatty Acids Synthase (FAS), Sterol Responsible Binding Protein-1c (SREBP-1c), Pyruvate Kinase (PK), Phosphoenol Pyruvate Carboxy Kinase (PEPCK) and Glucose Transporter 2 (GLUT-2) in liver. Therefore, the aim of present work is to speculate the interaction between cinnamon and diabetes through alteration in the expression of enzymes which regulate both lipid (FAS, LPL, HSL and SREBP1c) and carbohydrate metabolism (PK, PEPCK and GLUT2) in STZ Wistar rats.

2. MATERIAL AND METHODS

2.1. Materials

Streptozotocin (STZ) was obtained from sigma Aldrich, USA. The Wistar albino rats were from Egyptian Co. for Experimental Animals Import, Helwan, Egypt. Vehicles and related materials were from ADWIA pharmaceutical company, Egypt. Oligo dT, chloroform, ethanol and cytokines primers were from Wako pure chemicals, Osaka, Japan. TriZol reagent was from Invitrogen, Carlsbad, CA.

2.2. Cinnamon Extract Preparation

Cinnamon extract was extracted based on the method of (Sheng et al., 2008; Soliman et al., 2012). Briefly, cinnamon powder (100 g) was dissolved in 1000 mL double distilled water then subjected for revolving evaporator in vacuum state using vacuum pump till the volume of water reduced to 50%. The supernatant was filtered through Whatman paper no. 1 to obtain cinnamon water extract. The final CE concentration was measured by Lowry method for protein concentration.

2.3. Induction of Diabetes in Wistar Rats and Experimental Procedures

Adult Wistar rats weighting 200-250 g (90 days old) were used for conducting the experiment. A group of rats were injected intraperitoneally (ip) with STZ at the dose of 60 mg kg\(^{-1}\) body weight. The other group injected with water and received water orally and daily for 2 months and considered as a control group. STZ induced diabetes within 3 days after injection as confirmed by the increase in blood glucose levels. Rats with glucose levels over 200 mg dL\(^{-1}\) were considered as diabetic rats and were used for experiments. Next, diabetic rats were divided into control diabetic group received water and cinnamon diabetic treated group received cinnamon extract at a dose of 200 mg kg\(^{-1}\) body weight (Kim et al., 2006; Kim and Choung, 2010) orally and daily for 2 months. At the end of the experiment, rats were killed by decapitation and blood was collected to get plasma. Liver samples were immediately immersed in TriZol reagent and kept at -70°C until RNA extraction.

2.4. RT-PCR Analysis and Gene Expression

Homogenization of 50 mg of frozen tissue samples was carried after addition of 1 mL TriZol (Invitrogen, Carlsbad, CA) using a Polytron 300 D homogenizer (Brinkman Instruments, Westbury, NY).
Table 1. PCR conditions for genes of carbohydrate and lipid metabolism

| gene & product size | Forward primer | Reverse primer | Annealing temperature |
|---------------------|----------------|----------------|-----------------------|
| HSL313bp           | 5'-TGCCCAGGAGTGTCTGAG-3' | 5'AGGACACCTTGGCTTGAGCG-3' | 40 cycles, 61°C 1 min |
| LPL 269 bp         | 5'-CCTGATGACGCTGATTTGTG-3' | 5'TATGCTTCTGGGGGTTCCTTTGAT-3' | 24 cycle, 60°C 45 sec |
| PK 229 bp          | 5'ATTGCTGTGACTGAGTCTGC-3' | 5'GCCGATGATGTGGTTATAG-3' | 30 cycle, 52°C 1 min |
| PEPC 236 bp        | 5'TTACTGGGAAAGGCATCGAT-3' | 5'TCGTAGACAAAGGGGCAC-3' | 30 cycle, 52°C 1 min |
| GLUT2-2 330 bp     | 5'-AAGGATCAAAGCCATGTGG-3' | 5'-GGAGACCTCCTGCTCAGTG-3' | 30 cycle, 55°C 1 min |
| FAS 345 bp         | 5'-CCAGGACCAGACAGAAGA-3' | 5'-GACGCCAGTTGTTCGCC-3' | 30 cycle, 56°C 1 min |
| IGF 376 bp         | 5'GTAGGCTTGTCTTCCGCAC-3' | 5'GCACCTCTCTACCTCGCC-3' | 40 cycles, 58°C 1 min |
| SREBP-1c 191 bp    | 5'GGAGCCATGGATTGCACT-3' | 5'AGGAAGGCTTCAGAGGGA-3' | 33 cycle, 58°C 1 min |
| Resistin 220 bp    | 5'-CCTCTTCCTTTCTCTCC-3' | 5'-TGAGGACGGTTGATGGAA-3' | 30 cycles, 58°C 1 min |
| GAPDH (309 bp)     | 5'-AGATCCACAACGGGATCATT-3' | 5'-TCCCTCAAGATTGCAGCAA-3' | 25 cycles, 52°C 1 min |

PCR cycle of respective genes are shown, while temperature and time of denaturation and elongation steps of each PCR cycle are 94°C, 30 s and 72°C, 60 s, respectively.

Table 2. Changes in insulin, glucose and lipid profiles in normal, diabetic and diabetic plus cinnamon extract administered Wistar rats

| Parameter          | Control          | Diabetic         | Diabetic plus cinnamon extract |
|--------------------|------------------|------------------|-------------------------------|
| Glucose (mg/dL)    | 90.7±8.53        | 320.1±20.5*      | 108.5±6.2*                    |
| Insulin (mIU/mL)   | 5.2±0.4          | 2.7±0.07*        | 8±1.01*                       |
| Triglycerids (mg/dL)| 70.4±2.1        | 120.8±2.6*      | 71.5±1.5*                     |
| Cholesterol (mg/dL)| 95.5±9.1         | 147.4±12.6*     | 90.5±9.7*                     |
| VLDL (mg/dL)       | 25.7±2.9         | 32.6±2.7*       | 29.2±1.9*                     |
| HDL (mg/dL)        | 35.4±3.9         | 28.2±3.5*       | 33.1±2.5*                     |

Data are presented as (means ± S.E.). S.E = Standard error for 5 rats per each group. *p<0.05 Vs control and #p<0.05 Vs diabetic rats.

Total RNA was extracted from tissue homogenate via chloroform extraction followed by nucleic acid precipitation with isopropanol. The pellet was washed with 75% ethanol and resuspended in molecular biology grade water. Nucleic acid concentration was determined spectrophotometrically by measuring O.D at 260 nm (Smart-Spec; Bio-Rad Laboratories, Hercules, CA) and RNA integrity was evaluated using an Agilent bioanalyzer (model 2100; Agilent Technologies, Foster City, CA).

For CDNA synthesis, total RNA (1 µg) was denatured at 72°C for 5 min and then reverse transcribed using 100 units of Moloney Murine Leukemia virus reverse transcriptase (Gibco), 50 pmol of oligo (dT) primer and 20 nmol of dNTPs in a total volume of 10 µL at 37°C for 1 h followed by heating at 94°C for 5 min. PCR amplification was performed with 2.5 units Taq DNA polymerase (Perkin-Elmer, Foster City, CA, USA), 3 mM MgCl2 and 50 pmol of forward and reverse primers specific for respective genes in a total volume of 50 µL. The PCR conditions and primers sequence for different examined genes are listed in Table 1. PCR products were electrophoresed in 1.5% agarose gel stained with ethidium bromide and visualized under UV lamp.

2.5. Statistical Analysis

Results are expressed as means ± S.E. of independent experiments. Statistical analysis was done using ANOVA and Fischer’s post hoc test, with p<0.05 being considered as statistically significant.

3. RESULTS

3.1. Effect of CE Administration on Lipid Parameters and Glucose Levels in Diabetic Wistar Rats

STZ induced diabetic rats showed significant increase in cholesterol, TG, VLDL and decrease in HDL compared to normal rats. Meanwhile, administration of CE significantly (p<0.05) restored their levels to normal (Table 2). Concerning plasma insulin level in STZ diabetic rats, there was a decrement due to destruction of β-cells. Meanwhile, CE administration increased insulin and even higher than control. Results of insulin was reflected on glucose level which was higher in diabetic rats and normalized in CE administered rats compared to control (Table 2).
Fig. 1. RT-PCR analysis of FAS, LPL, HSL, SREBP-1c and resistin in liver and epididymal fat tissue of rats. Cinnamon was administered for STZ rats for 2 months as described in materials and methods. RNA was extracted and reverse transcribed (1 µg) and RT-PCR analysis was carried out for FAS, LPL, HSL, SREBP-1c and resistin genes.

Fig. 2. RT-PCR analysis of PEPCK and PK expression in liver of rats. Cinnamon was administered for STZ rats for 2 months as described in materials and methods. RNA was extracted and reverse transcribed (1 µg) and RT-PCR analysis was carried out for PEPCK and PK genes.
3.2. Effect of CE Administration on Gene Expression of Lipid Metabolism in Liver Tissues

To investigate the alteration in lipid metabolism by CE, mRNA from liver tissue was subjected for RT-PCR analysis. As shown in Fig. 1a, diabetes inhibited FAS mRNA expression and CE administration for 2 months normalized FAS expression to the normal control level. Moreover, there was an increase in mRNA expression of both LPL and HSL in diabetic rats. These increments were inhibited by administration of CE (Fig. 1b and c). Concerning SREBP1c mRNA expression in liver tissues, diabetic rats show decrement in mRNA expression. CE administration normalized SREBP1c expression compared to diabetic group (Fig. 1d and e). Resistin expression increased in diabetic rats and CE administration returned that increase to normal control expression.

3.3. Effect of CE Administration on PK and PEPCK Gene Expression in Liver Tissues

Next, we investigated the alteration in some enzymes regulating glucose metabolism including Pyruvate Kinase (PK) that is responsible for glycolysis and Phosphoenol Pyruvate Carboxykinase (PEPCK) that is involved in gluconeogenesis. The expression of hepatic PK mRNA as estimated by RT-PCR analysis was significantly decreased in diabetic rats (Fig. 2a). Administration of CE to diabetic rats resulted in reversal PK expression. Parallel to those findings, there was an increase in
hepatic PEPCK mRNA expression in diabetic rats compared to control rats (Fig. 2b) and administration of CE for 2 months normalized the PEPCK mRNA levels of CE administered diabetic rats.

3.4. Effect of CE Administration on GLUT2 and IGF Gene Expression in Liver Tissues

Since insulin was decreased in diabetic rats and CE administration normalized the increase in glucose, we tested the physiological importance of insulin dependent GLUT2 translocation. As shown in Fig. 3a, diabetic rats showed an increase in GLUT2 mRNA expression and that increase was inhibited after CE administration in a way to regulate the excessive hepatic glucose utilization. Finally, we tested the changes in Insulin like Growth Factor (IGF) mRNA expression. As shown in Fig. 3b, IGF expression was significantly decreased in diabetic rats and normalized and increased after CE administration for 2 months to react with hyperglycemia of diabetic rats.

4. DISCUSSION

Diabetes is a chronic metabolic disorder that affects approximately 3% of population worldwide (Kim et al., 2006). Gaster and Hirsch (1998) reported that sustained reductions in hyperglycemia will decrease the risk of developing microvascular diseases and reduce diabetes complications. Usage of oral hypoglycemic drugs to treat diabetes has several limitations, such as adverse effects and high rates of secondary failure (Kim et al., 2006). Those adverse effects forced the diabetic patients to use herbal medication that has a similar degree of efficiency without side effects and that is the purpose of this study. We have shown in this study that administration of cinnamon extract to STZ diabetic rats induced insulin mimetic effects. The results showed that, insulin deficiency is strongly associated with metabolic dyslipidemia in diabetes and obesity. Moreover, Qin et al. (2010) reported that the use of water-soluble CE improved the metabolic syndrome by regulating the circulating adipose-derived factors and multiple genes related to carbohydrate metabolism and lipogenesis. Our findings have shown the anti-diabetic activity of CE in STZ diabetic rats. CE administration not only reduced blood glucose levels (320.1±20.5 for diabetic rats Vs. 108.5±6.2 for CE plus Diabetes) after 2 months but also normalized and restored insulin levels in diabetic rats (2.7±0.07, 8±1.01 for diabetic and CE plus diabetes respectively) compared to initial insulin control values. Parallel findings were reported by Anand et al. (2010) and Subash Babu et al. (2007) who reported that 45 days treatment of cinnamaldehyde increases serum insulin levels in STZ induced diabetic rats. This finding was explained that the over insulin secretion from still working β cell in a way to overcome hyperglycemia of diabetic rats (Kim et al., 2006).

To understand the molecular mechanism of CE actions, we examined the mRNA expression of genes involved in lipid and glucose metabolism in liver of diabetic rats. Administration of STZ diabetic rats with CE induced significant decrease in LPL, HSL and a significant increase in resistin. Also, the normalization in lipid parameters in blood is associated with the increase in lipids synthesizing enzymes expression in diabetic treated with CE. Because resistin is known to be a potent lipolytic protein and increased peripheral glucose utilization (Ahima and Flier, 2000; Kim and Choung, 2010; Wanders et al., 2010). CE administration decreased glucose levels in STZ diabetic rats with stimulation of insulin production like effects and that confirmed by increase in plasma insulin levels. The possible mechanism may be through increasing either the pancreatic secretion of insulin from the existing beta cells or its release from the bound form (Kim et al., 2006). CE might improve diabetes by normalizing the fasting blood glucose level as well as postprandial plasma glucose level (Kim et al., 2009). In turn, in hyperinsulinemia, cinnamon increases insulin sensitivity for effective glucose disposal in rats although in humans cinnamon does not appear to improve fasting blood glucose levels and lipid parameters in patients with type 1 or type 2 diabetes (Baker et al., 2008). Here, CE improved and normalized the changes in lipid parameters as TG, cholesterol and HDL and that was parallel with results of Khan et al. (2003); Kim and Choung (2010) and Qin et al. (2003) and improved insulin resistance induced by feeding high fat diet (Thorens, 1996). CE ameliorates hyperglycemia in vitro as insulin secretion studies were carried out using isolated rat primary islet culture. CE acts by enhancing release of insulin through β cells stimulation as CE exerts a direct insulin releasing effect (Sharma et al., 2006; Rokeya et al., 1999; Bolkent et al., 2000).

For our knowledge, cinnamon effects on gene expression of lipogenesis and fatty acids biosynthesis not widely examined. SREBP-1c preferentially enhances transcription of genes required for fatty acid
synthesis but not cholesterol synthesis (Horton et al., 2002). Huang et al. (2011) suggested that CE exerts antiadipogenic effects through modulation of the PPAR-γ and AMPK signaling pathways. Our results are in accordance with those of Khan et al. (2003), CE induced lowering glucose, total cholesterol, VLDL and triglyceride levels in diabetic subjects. During diabetes the expression of FAS and SREBP-1c (Fig. 1) decreased because lipogenesis is impaired due to disturbance in insulin levels but CE administration re-increased and normalized their expression level confirming CE role in regulation of lipogenesis. In parallel, the expression of LPL and HSL increased during diabetes in a way to support body with source for energy through fatty acids oxidation (Shimano et al., 1999). But the CE administration to diabetic rats normalized significantly that increases (LPL and HSL) to normal non diabetic rats confirming the antilipolytic activity of CE. Sheng et al. (2008) reported an increase in LPL and GLUT4 expression and cinnamon in its water extract form can act as a dual activator of PPAR gamma and alpha and may be an alternative to PPAR gamma activator in managing obesity-related diabetes and hyperlipidemia. Moreover, Lee et al. (2003), reported that dietary cinnamate inhibits hepatic HMG-CoA reductase activity, resulting in lower hepatic cholesterol content and suppresses lipid peroxidation via enhancement of hepatic antioxidant enzyme activities and that is coincided with our results.

Glycogen is the storable form of glucose inside cells especially in liver and skeletal muscles and its accumulation indicates direct reflection of insulin activity since it regulates glycogen deposition by stimulating glycogen synthase and inhibiting glycogen phosphorylase (Kruszynska et al., 1998; Kruszynska and Olefsky, 1996; Thorburn et al., 1991). STZ causes destruction of β cells of pancreas resulting in marked decrease in insulin levels, it could be predicted that glycogen levels in tissues (muscle and liver) decrease as the influx of glucose in liver is inhibited in the absence of insulin and recovers on insulin treatment (Vats et al., 2004). Our findings showed that administration of diabetic rats with CE induced significant increase in PK and a decrease in PEPCK expression in diabetic rats. That means in diabetic rats CE improved PK and PEPCK enzyme expression levels, both are the major enzymes contributed to glucose homeostasis. PEPCK, which catalyzes a regulatory step in gluconeogenesis, is one of the key enzymes of hepatic carbohydrate metabolism and insulin deficiency is clearly associated with changes in hepatic metabolism including increased expression of PEPCK (Jomain-Baum and Schramm, 1978). In our study, CE reversed the increase of hepatic PEPCK mRNA expression in STZ diabetic rats and this attenuation of the hepatic PEPCK mRNA expression was associated with plasma glucose-lowering activity of CE (Anand et al., 2010). So we conclude that CE exerts its glucose-lowering effect mainly through an enhancement of glucose utilization of skeletal muscle and a reduction of hepatic gluconeogenesis. Several potential herbal plant extract and purified compounds have been shown to improve the diabetic condition (Sharma et al., 2008). The PK activity decreases as the result of diabetes and increases by the administration of insulin to diabetic rats in the liver tissues (Yamada and Noguchi, 1999). The altered activity during diabetic conditions could be expected to diminish the metabolism of glucose and ATP production. The decrease in activity of PK in the liver tissue of streptozotocin diabetic rats is the cause of reduced glycolysis and amplified gluconeogenesis as indicated by PEPCK expression (Taylor and Agius, 1988). Parallel with PK and PEPCK, is the pattern of IGF and GLUT2 expression. GLUT2 is a transmembrane carrier protein that enables passive glucose movement across cell membranes. It is the principal transporter for transfer of glucose between liver and blood and for renal glucose reabsorption (Freitas et al., 2005). IGFs are proteins with high sequence similarity to insulin. IGFs are part of a complex system that cells use to communicate with their physiologic environment, since at high concentrations is capable of activating the insulin receptor, it can also complement for the effects of insulin (Scarth, 2006). In our study, the normalization of GLUT2 expression after CE administration may be a reflect pathway to reverse the glucose uptake in liver cells while CE administration increases IGF expression to induce insulin like effects.

5. CONCLUSION

We can conclude that cinnamon extract induce beneficial effects in STZ diabetic rats and affect the genes related to carbohydrate (PPECK, PK, GLUT-2 and IGF) and lipid metabolism (FAS, LPL, HSL and SREBP-1c) in a way to control the metabolic biohazards
accompanied diabetes. Moreover, CE is a good herbal medication with insulin mimetic activity.

6. ACKNOWLEDGMENT

This study was supported by Taif University of Kingdom of Saudi Arabia (Research project number 1051-1-1432).

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