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Effects of Parboiled Rice Diet on Oxidative Stress Parameters in Kidney of Rats with Streptozotocin-Induced Diabetes

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ABSTRACT The effect of parboiled rice (PR) and white rice (WR) diets on oxidative stress (OS) parameters was investigated in the kidneys of rats with streptozotocin-induced diabetes (40 mg kg^{-1}, iv). The experimental groups ($n=8$) were control fed with PR (CPR), control fed with WR, diabetic fed with PR, and diabetic fed with WR. After 30 days of treatment, all animals were anesthetized and exsanguinated before removal of kidneys, which were used to determine thiobarbituric acid reactive substances (TBARS), lipid hydroperoxides, carbonyl protein, superoxide dismutase, catalase, glutathione peroxidase (GPx), glutathione reductase, glutathione-S-transferase activities, and levels of glutathione (GSH). Total phenolic compounds were determined in WR and PR grains. Our data indicated that diabetes induced increase in TBARS and lipid hydroperoxides levels. Although PR has not prevented the rise in the levels of these measurements, its consumption by our animals resulted in higher GPx activity and GSH content than that of the CPR. Moreover, PR also presented concentration of total phenolic compounds 127% higher than WR grains. Thus, its consumption in this diabetic condition is suggested because this seems to confer greater protection against OS in the renal tissue of diabetic animals.

KEY WORDS: • *diabetes* • *kidney* • *oxidative stress* • *parboiled rice* • *white rice*

INTRODUCTION

Rice (*Oryza sativa* L.) is one of the main foods in the human diet, being consumed by approximately half of the world, preferably in the form of white rice (WR).[1] However, consumption of parboiled rice (PR), which is more resistant to polishing and has nutritional advantages due to the retention of minerals and water-soluble vitamins, is growing.[2,3] Several studies have shown that supplementing the diet with colored pericarp rice decreases oxidative stress (OS) *in vivo*.[4]

OS occurs when there is an increased generation of reactive oxygen species (ROS), decrease in antioxidant defenses, or a combination of both.[5] ROS are formed during the metabolism of oxygen, and their concentrations are controlled by antioxidant defenses, which include several enzymatic and nonenzymatic systems. The enzymatic ones include enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione-S-transferase (GST). SOD converts the superoxide anion formed from molecular oxygen into hydrogen peroxide (H_2O_2), which is converted to water and oxygen by the action of CAT. GPx, in turn, catalyzes the conversion of both H_2O_2 and organic hydroperoxides to less reactive products, employing for that glutathione (GSH) in its reduced form as electron donor. The oxidized form of glutathione is again reduced by the action of glutathione reductase (GR) and NADPH as electron donor. GST has the main role in elimination of exogenous substances and some of them act eliminating organic hydroperoxides. ROS are highly reactive and can lead to oxidative damage to macromolecules such as lipids, proteins, and DNA. Thus, these species have been involved in the pathophysiology of diabetes mellitus (DM).[6]

An experimental model for the study of DM is the administration of streptozotocin (STZ) in rats, which develop diabetic nephropathy (DN).[7] Some studies have shown that supplementation of diet with antioxidants such as phenolic compounds present in plants attenuate ROS-mediated DN by reducing ROS production.[8] Although rice is not among the foods with the highest concentration of phenolic compounds, it behaves as a source of these compounds due to its large consumption. As PR has special nutritional and

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functional characteristics when compared to WR, this type of rice can be considered a value-added product, deserving therefore more attention from industry, researchers, and nutrition professionals.[2] Thus, this study compared the effect of a diet of PR to a diet of WR on OS parameters in kidney of rats with DM induced by STZ. Our hypothesis is that substances present in PR rice could reduce the OS and consequently attenuate DN.

MATERIALS AND METHODS

Rice samples

The samples of PR and WR, both polished, were obtained from local traders. They were submitted to the cooking process and drying as described by Helbig *et al*.[9] After cooking, the grains were transferred to polyethylene sieves and dried in an oven with forced air for 24 h at 60°C. Next, the grains were ground and sieved to obtain flour.

Diets

The rice flours, parboiled and white, were added to the diets of rats, whose formulation is consistent with the guidelines of the American Institute of Nutrition for growing rats (AIN-93G), being isoenergetic.[10] The centesimal composition was determined in both samples of flour and in the experimental diets.[11] Diets were fed to animals as pellets. Diet composition is shown in Table 1.

Animals

Adult male Wistar rats, weighing 293 ± 5 g on average, were obtained from the Central Animal Breeding Facility of the Federal University of Santa Maria, RS, Brazil. The study was also approved by the Ethics Committee of the Federal University of Santa Maria (process 051/2009). The animals were kept in cages under controlled temperature (23°C ± 2°C) and light–dark cycle of 12 h with water and food *ad libitum*.

Experimental protocol

Rats ($n = 32$) were randomly divided into four groups with eight animals each: control group fed a diet of PR (CPR), control group fed a diet of WR (CWR), diabetic group fed a diet of PR (DPR), and diabetic group fed a diet of WR (DWR). Treatment with the different diets was initiated after confirmation of DM by plasma glucose determination. This occurred 9 days after STZ administration. Animals' food consumption was monitored on a daily basis and their body weights were recorded weekly to determine the food efficiency ratio (FER) by using the body weight gain for experimental period and (g) food intake for experimental period (g) ratio. The treatment lasted 30 days.

Table 1. Composition of the Diets

Component	*PR (g kg^{-1})*	*WR (g kg^{-1})*
WR flour	0	582
PR flour	582	0
Casein	153	151
Sucrose	100	100
Soybean oil	65	67
Cellulose	50	50
Mineral mix (AING-93MX)	35	35
Vitamin mix (AING-93VX)	10	10
L-cistine	3	3
Choline bitartrate	2.5	2.5
Tert-butylhydroquinone	0.014	0.014

PR, parboiled rice diet; WR, white rice diet.

Induction of DM

DM was induced by administration of a single dose of STZ in the tail vein at a dose of 40 mg kg^{-1} body weight. STZ was diluted in 0.01 M sodium citrate buffer, pH 4.5. Animals in control groups received a single dose of sodium citrate buffer 0.01 M, pH 4.5, at the same conditions used for STZ administration.[12] The development of DM was confirmed by measurement of plasma glucose 9 days after STZ administration. Only rats with plasma glucose levels above 11.1 mmol l^{-1} were considered diabetic and used in the study.

Blood analysis

Blood samples of rats in the different experimental groups were collected from the retro-orbital plexus 1 day before induction, 9 days after induction, and 30 days after starting treatment. At the end of 30 days, the animals were anesthetized with xylazine and ketamine and sacrificed by exsanguination. Immediately after collection, blood was centrifuged at 1800 *g* for 15 min at 4°C to obtain plasma. Glucose, total cholesterol, triglycerides, and plasma creatinine levels were determined by using commercial kits (Labtest).

Tissue homogenate preparation

Immediately following exsanguination, the kidneys were removed, cleaned, and washed in ice-cold normal saline. The kidney was homogenized in 1.15% (w/v) potassium chloride containing 1 mM phenylmethylsulfonyl fluoride. The homogenates were centrifuged at 700 *g* for 10 min at 4°C to discard nuclei and cell debris, and the supernatant fraction obtained was frozen at −70°C for further measurements.[13]

Oxidative damage measurements

Lipid peroxidation (LPO) was measured by the determination of lipid hydroperoxides with a modified version of the method by Jiang *et al*.[14] This technique can detect the primary products of peroxidation, using Fe^{2+} oxidation by lipid hydroperoxides in acid medium in the presence of xylenol orange dye, forming a complex with Fe^{3+}. Reading was performed in spectrophotometer at 560 nm. Results are reported as nmol mg protein^{-1}. LPO was also estimated by the thiobarbituric acid reactive substances (TBARS) assay.[15] Results were expressed as nmol mg protein^{-1}.

Protein oxidation was performed by carbonyl assay, and the results were expressed as nmol mg protein^{-1}.[16]

Antioxidant enzyme activities

SOD activity, expressed as USOD mg protein^{-1}, was based on the inhibition rate of autocatalytic adenocrome generation at 480 nm.[17] CAT activity was determined by following the decrease in the 240 nm absorption of the H_2O_2. It was expressed as pmol mg protein^{-1}.[18] GPx activity was measured by following an NADPH oxidation at 340 nm as described by Flohé and Gunzler,[19] and the results were expressed as μmol min^{-1} mg protein^{-1}. GST activity, expressed as pmol min^{-1} mg protein^{-1} of protein, was measured by the rate of formation of dinitrophenyl-*S*-glutathione at 340 nm.[20] GR activity was expressed as μmol min^{-1} mg protein^{-1} of protein at 340 nm as described by Carlberg and Mannervik.[21]

Nonenzymatic antioxidant (Tissue sulfhydryl groups)

Tissue sulfhydryl groups (GSH) were measured at 412 nm after reaction with 5,5′-dithiobis-(2-nitrobenzoic acid). Proteins were eliminated through the addition of 0.5 M perchloric acid.[22] The thiol content was expressed in nmol protein^{-1}.

Protein measurement

The protein content was measured by the method of Bradford.[23]

Extract preparation

Extractions were performed by using the method described by Pérez-Jiménez and Saura-Calixto.[24] The procedure was conducted in triplicate, and the extracts were used for determination of total phenolic compounds.

Determination of total phenolic compounds

The total phenolic compounds were determined according to the Folin-Ciocalteau procedure.[25] The absorbance of the resulting blue color was measured at 765 nm. Gallic acid was used as a standard, and the results were expressed as gallic acid equivalents (mg GAE) 100 g of grain (dry weight)$^{-1}$. The reaction was conducted in triplicate.

Statistical analysis

The results are expressed as the mean ± standard error (S.E.). Student's *t*-test was used for comparison of means regarding determination of total phenolic compounds. Other means were compared by the two-way analysis of variance followed by Duncan's multiple range test. All analyses were performed by using Statistica 5. Differences were considered significant at $P < .05$.

RESULTS

Body weight, weight gain, food intake, and FER

Diabetic animals had a reduction in body weight, weight loss, increased food intake, and decreased FER when compared to control groups ($P < .001$). The data also show that PR consumption by the animals of the DPR group attenuated the changes observed in weight gain and FER when compared to DWR ($P < .05$) (Table 2).

Renal hypertrophy

The ratio of kidney weight to body weight was calculated in different experimental groups to estimate renal hypertrophy. There was a significant increase in this ratio in the diabetic animals as compared to controls ($P < .001$). Among diabetic rats, those of the DPR group showed less pronounced hypertrophy when compared to DWR ($P < .05$) (Table 2).

Blood analysis

In diabetic rats, the plasma concentrations of glucose ($P < .001$) and creatinine ($P < .05$) were significantly higher than in their respective control groups. Among the diabetic rats, glucose values were higher in DWR than DPR group (34%) ($P < .05$) (Table 3).

Oxidative damage

The changes in oxidative damage markers are summarized in Table 4. Results indicate an increase in hydroperoxide

Table 2. Effects of Different Rice Diets on Body Weight, Kidney Weight and Body Weight Ratio, Weight Gain, Food Intake and Food Efficiency Ratio of Control and Diabetic Rats

Parameter	*CPR*	*CWR*	*DPR*	*DWR*
Body wt (g)	346.8 ± 11.1	351.0 ± 11.0	256.7 ± 14.1[a]	238.2 ± 13.2[a]
Kidney wt/body wt (mg g^{-1})	5.9 ± 0.3	6.5 ± 0.1	11.2 ± 0.1[a,b]	12.3 ± 0.3[a]
Weight gain (g)	64.5 ± 12.1	66.5 ± 5.2	− 45.2 ± 9.0[a,c]	− 84.0 ± 11.4[a]
Food intake (g)	17.2 ± 0.4	18.8 ± 0.5	30.3 ± 0.9[a]	33.0 ± 0.9[a]
FER	3.0 ± 0.1	3.6 ± 0.1	− 1.5 ± 0.2[a,c]	− 2.5 ± 0.3[a]

The data appear as the mean ± SE ($n = 8$).

[a]Denotes that data are significantly different from respective control at $P < .001$.

[b]Denotes that data are significantly different from DWR at $P < .01$.

[c]Denotes that data are significantly different from DWR at $P < .05$.

FER, food efficiency ratio; CPR, control group fed with parboiled rice diet; CWR, control group fed with white rice diet; DPR, diabetic group fed with parboiled rice diet; DWR, diabetic group fed with white rice diet.

Table 3. Effects of Different Rice Diets on Plasmatic Glucose, Cholesterol, Triglycerides, and Creatinine Levels of Control and Diabetic Rats

Parameter	*CPR*	*CWR*	*DPR*	*DWR*
Glucose (mmol L^{-1})	5.5 ± 0.3	6.0 ± 0.5	21.3 ± 1.3[ab]	28.7 ± 1.0[a]
Cholesterol (mmol L^{-1})	1.3 ± 0.1	1.3 ± 0.1	1.4 ± 0.1	1.4 ± 0.1
Triglycerides (mmol L^{-1})	0.39 ± 0.04	0.45 ± 0.06	0.42 ± 0.03	0.48 ± 0.07
Creatinine (μmol L^{-1})	45.4 ± 1.8	45.4 ± 2.1	53.6 ± 1.5[c]	55.1 ± 1.7[c]

The data appear as the mean ± S.E. ($n = 8$).

[a]Denotes that data are significantly different from respective control at $P < .001$.

[b]Denotes that data is significantly different from DWR at $P < .001$.

[c]Denotes that data are significantly different from respective control at $P < .05$.

levels, determined by xylenol orange, in all diabetic groups as compared to their respective controls ($P < .001$). Lipid peroxides measured by TBARS showed increased values in all diabetic groups as compared to their respective controls, regardless of the diet they had received. In diabetic rats, TBARS also showed higher levels in the DWR group than in the DPR (26%) ($P < .05$). The WR treatment of diabetic rats also resulted in increased kidney oxidative damage to proteins measured using the carbonyl assay (44%) as compared to the respective control ($P < .01$).

Antioxidant enzyme activities

The results of antioxidant enzyme activities in the kidneys of diabetic and control rats fed with rice diets are shown in Table 5. SOD activity in the DWR group fell by 30% as compared to CWR ($P < .05$). The DWR group also presented a decrease of 30% in SOD activity as compared to DPR ($P < .05$). CAT activity was reduced by 25% in the DWR group as compared to CWR under the same experimental conditions ($P < .05$). Among diabetic rats, those of the DWR group showed a decrease of 27% in CAT activity as compared to DPR ($P < .05$). Diabetic rats of the DPR group showed an increase of 25% in GPx activity as compared to CPR ($P < .05$). In diabetic animals, the DPR group also showed an increase of 19% as compared to DWR ($P < .05$). GR activity decreased by 29% in diabetic rats of the DWR group as compared to CWR ($P < .05$).

Nonenzymatic antioxidant (tissue sulfhydryl groups)

GSH values increased in the DPR group when compared to CPR (29%) ($P < .05$). In DWR, GSH values decreased by 24% as compared to CWR ($P < .05$). In diabetic rats, DPR showed an increase of 60% in the GSH content as compared to DWR ($P < .05$) (Table 5).

Total phenolic compounds

The rice samples analyzed showed different concentrations of total phenolic compounds (Table 6), which were 127% higher in PR than in WR grains ($P < .01$).

DISCUSSION

Our results showed that diabetic condition in rats treated with a single dose of STZ was successfully achieved as observed from the elevation in plasma glucose levels, reduction in body weight, increase in food intake, decrease in FER ratio, development of hypertrophy, and increase in creatinine values. These data are similar to those described in the literature.[26,27]

It was reported that hyperglycemia induces OS in the rat kidney[28] and that increased OS in this tissue may contribute to the development of DN.[29] Potential causes of increased OS in DM include increased production of ROS, decreased antioxidant activity and reduced levels of GSH, and other nonenzymatic antioxidants.[30]

Several studies have suggested that ROS occurring in experimental DM exert their cytotoxic effects on phospholipids membranes, increasing LPO[31] in kidney tissue.[8] In this study, we observed an increased renal LPO in diabetic animals, mostly in that of DWR group, as demonstrated by lipid hydroperoxides and TBARS assessments. Lipid hydroperoxides detected by xylenol orange arise from the damage caused by LPO in its early stage, while the final products of LPO are seen through TBARS. In plasma of diabetic rats, increased LPO was demonstrated through higher TBARS and lipid hydroperoxides levels.[32] Besides, clinical studies using the xylenol orange assay reported that plasma lipid hydroperoxide levels are substantially higher in diabetic patients compared with control subjects.[33] Our

Table 4. Effects of Different Rice Diets on Oxidative Damage of Control and Diabetic Rats

Parameter	*CPR*	*CWR*	*DPR*	*DWR*
TBARS (nmol mg $protein^{-1}$)	0.37 ± 0.02	0.37 ± 0.02	0.64 ± 0.05[ab]	0.81 ± 0.07[a]
Lipid hidroperoxides (nmol mg $protein^{-1}$)	2.2 ± 0.2	2.4 ± 0.3	9.7 ± 0.8[c]	11.6 ± 0.9[c]
Carbonyl protein (nmol mg $protein^{-1}$)	4.6 ± 0.3	4.7 ± 0.6	5.7 ± 0.4	6.8 ± 0.2[a]

The data appear as the mean ± S.E. ($n = 8$).

[a]Denotes that data are significantly different from respective control at $P < .01$.

[b]Denotes that data are significantly different from DWR at $P < .05$.

[c]Denotes that data are significantly different from respective control at $P < .001$.

TBARS, thiobarbituric acid reactive substances.

Table 5. Effects of Different Rice Diets on Antioxidant Enzyme Activities and Nonenzymatic Antioxidant Concentrations of Control and Diabetic rats

Parameter	*CPR*	*CWR*	*DPR*	*DWR*
SOD (USOD mg protein^{-1})	4.2 ± 0.3	4.4 ± 0.1	4.4 ± 0.3[a]	3.1 ± 0.4[b]
CAT (pmol mg protein^{-1})	2.8 ± 0.2	2.9 ± 0.2	2.8 ± 0.1[a]	2.2 ± 0.1[c]
GPx (μmol min^{-1} mg protein^{-1})	0.20 ± 0.01	0.21 ± 0.01	0.25 ± 0.01[ab]	0.21 ± 0.01
GR (μmol min^{-1} mg protein^{-1})	0.062 ± 0.005	0.065 ± 0.001	0.055 ± 0.003	0.046 ± 0.002[a]
GST (pmol min^{-1} mg protein^{-1})	2.3 ± 0.2	2.6 ± 0.1	2.9 ± 0.1	2.9 ± 0.3
GSH (nmol mg protein^{-1})	47.4 ± 2.7	48.3 ± 2.0	61.2 ± 3.4[ad]	36.9 ± 4.9[a]

The data appear as the mean ± S.E. ($n = 8$).
[a]Denotes that data are significantly different from DWR at $P < .05$.
[b]Denotes that data are significantly different from respective control at $P < .05$.
[c]Denotes that data are significantly different from respective control at $P < .01$.
[d]Denotes that data are significantly different from DWR at $P < .001$.
SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GR, glutathione reductase; GST, glutathione-S-transferase, GSH, sulfhydryl groups.

results also showed that enhanced renal protein oxidation occurred only in DWR by means of carbonyl groups measurement. An elevation of this protein oxidation marker was demonstrated in kidney of diabetic rats.[34]

In diabetic state, insulin deficiency causes the impairment of glucose utilization leading to an increased generation of superoxide anions.[6] SOD is an important defense enzyme specific to superoxide anions detoxification, responsible for decreasing the toxic effects caused by these radicals.[35] Studies have reported reduction of tissue SOD activities in STZ-induced diabetic rats.[36] Direct inhibitory effects caused by increased tissue-oxidant activity could reduce the tissue SOD activities.[37] Moreover, it was reported that reduced activity of CAT in STZ-induced diabetic animals results in accumulation of H_2O_2, which produces deleterious effects, such as increased LPO and oxidative damages to proteins.[38] These observations also may have contributed to the condition present in our DWR group.

GPx works together with GSH to metabolize H_2O_2 and hydroperoxides to nontoxic products at the expense of GR.[39] Various studies show that a characteristic of the diabetic state is the presence of impairment to the GPx system[38] and suggest damage to systems of nonenzymatic antioxidants, such as GSH.[40] An increased activity of GPx was found in our DPR group. This could be explained by the high content of GSH also observed in this diabetic group, since GSH is the main intracellular redox component, acting as substrate and cofactor of GPx.[41]

The highest antioxidant activity in rice occurs in whole grains and in those with red- and black- pericarp due to the higher concentration of polyphenols.[42] Since the presence of phenolic compounds is associated with the pericarp, it is possible that the increased resistance of PR grains to the removal of this structure during the rice polishing process may have resulted in the retention of more of these substances. We suggest that for this reason, our PR samples contained a higher concentration of total phenolic compounds in its composition.

Table 6. Total Phenolic Content of Parboiled and White Rice Grains

Sample	*Total phenolic content (mg GAE 100g dry wt^{-1})*
PR	25.06 ± 1.10
WR	11.01 ± 2.40[a]

The data appear as the mean ± S.E. ($n = 3$).
[a]Denotes that data are significantly different from PR at $P < .01$.
GAE, gallic acid equivalents.

In conclusion, our data showed that both types of rice have not prevented LPO determined by TBARS and hydroperoxide lipids measurements in the kidneys of STZ induced-diabetic rats. Nevertheless, the apparent benefits arising from the consumption of PR by diabetic rats were greater GPx activity and GSH levels. PR also showed a higher concentration of total phenolic compounds, which is probably associated with greater protection against OS in the renal tissue of diabetic animals, at least in this experimental condition of DM. On the other hand, DWR has showed higher TBARS levels than DPR, although this difference was not observed in the hydroperoxide lipids assessment. Moreover, WR consumption by diabetic animals seems to result in oxidative damage to proteins. These results could be associated with decreased amount of renal antioxidants in DWR group as a result of higher blood glucose levels also found in these animals. It could mean different degrees of renal injury and then varying degrees of pancreatic damage and higher ROS generation, which could explain the differences found in our results.

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AUTHOR DISCLOSURE STATEMENT

All authors read and approved the findings of the study. There are no conflicts of interest.

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