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Original Article

Comparative Effect of High Carbohydrate Diet and High Fat Diet on Brush Border Membrane Enzymes, Energy Metabolism, Transport Functions and Antioxidant Defense Mechanism in Superficial and Juxta-Medullary Cortex of Rat Kidney

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ABSTRACT

The study aimed to compare the effects of a diet rich in carbohydrates or fat on rat kidneys which play important role in the maintenance of body fluid volume., composition and pH by its absorptive functions. Rats were fed with a high carbohydrate (HCD), high fat (HFD) or normal diet (control) for 28 days. After the applications, blood samples were collected and the kidneys were removed under anesthesia. HCD and HFD increased but differentially serum glucose, cholesterol and phospholipids. Serum inorganic phosphate (Pi) was increased and urine Pi decreased but serum and urine creatinine were not affected by both HCD and HFD. Alkaline phosphatase (ALkPase) activity increased by HCD but decreased by HFD in brush border membrane vesicles (BBMV). The effect was greater in BBMV from superficial cortex (BBMV=SC) than in from juxtamedullary cortex (BBMV-JMC). However, γ-glutamyl transpeptidase (GGTase) activity was similarly lowered in BBMV-SC and BBMV-JMC by HCD and HFD. Kinetic studies revealed that increase/decrease of ALkPase activity by HCD /HFD was due to increase/decrease of Vmax and Km values. HCD increased enzymes of glycolysis and TCA cycle but decreased the enzymes of gluconeogenesis and HMP-shunt pathways in the renal homogenates. HFD lowers the enzymes of glucose metabolism but increased enzymes of gluconeogenesis. The BBM uptake of Pi was increased by HCD and HFD alike but the effect by HCD was more pronounced than by HFD. Both HCD and HFD increased lipid peroxidation (MDA) and decreased activity of superoxide dismutase and catalase in kidney tissues. In conclusion, consumption of both HCD and HFD increased oxidative stress that caused specific alteration in BBM enzymes, transport of Pi and metabolic activity and perturbed oxidant-antioxidant balance albeit differentially as indicated by the changes observed in relevant enzymes and other parameters.

Keywords: High carbohydrate diet, High fat diet, Kidney, Cortex, Medulla, Brush border membrane, Carbohydrate metabolism, Pi transport, Oxidative stress

Highlights

- Serum glucose, cholesterol, and phospholipids were increased by both HCD and HFD. Serum Pi increased but urine Pi decreased by both diets.
- The activity of BBM ALkPase was increased by HCD but decreased by HFD and GGTase activity was lowered by both HCD and HFD.
- HCD increased enzymes of glycolysis and TCA cycle but decreased the enzymes of gluconeogenesis and HMP-shunt. However, HFD lowers the enzymes involved in glucose degradation but increased enzymes of gluconeogenesis.
- BBM transport of Pi was increased by HCD and HFD alike due to increase of both Vmax and Km values but the effect on Pi uptake was more pronounced by HCD than by HFD.
- Both HCD and HFD induced oxidative stress and suppressed anti-oxidant enzymes in kidney tissues.
- The effect of HCD and HFD om various parameters was differentially observed in superficial cortex and juxtamedullary cortex

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Introduction

The relationship between diet and health is the subject of great controversy. Adequate and balanced nutrition is important to maintain health. Sugar and fat rich, fried and processed food cause negative impact on human health and lead to certain diseases like obesity, diabetes, cardiovascular diseases and cancer (1-3). Nutritional stress, starvation, malnutrition and dietary restrictions have been shown to alter structure, metabolic activity and functional capabilities of kidney, liver and intestine (4-7).

It is well known that the kidney plays important role in the maintenance of body fluid volume., composition and pH by its absorptive functions (8,9). The kidney is heterogenous structure consisting of distinct cortical, outer and inner medullary tissue zones which exhibit different structural, metabolic and functional properties due to differential nephron population and subsegments and oxygen tension (10-13). The cortex is the site for oxidative metabolism and gluconeogenesis whereas anaerobic glycolysis is prevalent in the medulla because of high and low oxygen tension (pO2), respectively (14). The proximal tubules are major metabolic and functional site where bulk of sodium (Na) and other ions, various solutes and water are reabsorbed across their luminal brush border membranes (BBM) which contains a number of hydrolytic enzymes and transport systems (8, 13, 15).

The kidney has the ability to adapt to the changes in the external and internal environment in acute situations for maximum work functions (16). Fasting, religious fasting and certain environmental factors have been shown to produce extensive changes in the metabolism, and transport functions of the kidney (7, 17-20). Recently, we have demonstrated that high carbohydrate (HCD) and high fat (HFD) diets caused differential effects on the structure and metabolic activity of rat intestine and liver in part due to increased oxidative stress (21).

In the present study we have investigated the effect of HCD and HFD on the enzymes of carbohydrate metabolism, brush border membrane (BBM), oxidative stress and on BBM transport of Pi in different renal tissues i.e. in whole (WC), superficial (SC) and juxtamedullary cortex (JMC) to assess the structural integrity, metabolic activity and functional capability of the kidney. Feeding of HCD and HFD increased serum glucose, cholesterol, phospholipids and Pi but decreased urinary Pi. The activity of BBM ALkPase was increased by HCD but decreased by HFD but GGTase activity was lowered by both HCD and HFD. HCD increased enzymes of glucose degradation but decreased the enzymes of gluconeogenesis. However, HFD lowers the enzymes involved in glucose degradation but increased enzymes of gluconeogenesis. Both HCD and HFD increased BBM transport of Pi and oxidative stress and decreased antioxidant enzyme activities although differentially in rat kidney tissues. In conclusion, consumption of both HCD and HFD caused extensive alterations in serum parameters, BBM enzymes activity, altered metabolic activity and decreased antioxidant defense mechanism albeit differentially as indicated by the changes observed in relevant enzymes and Pi transport capacity.

Materials and Methods

Wistar rats were purchased from All India Institute of Medical Sciences (New Delhi, India). ^{32}Pi was purchased from Bhabha Atomic Research centre (Mumbai, India). All other chemicals used were of analytical grade and were purchased from Sigma Chemical Co. (St Louis, MO, USA) unless otherwise stated.

Diet

Normal Control Diet (NCD):

The standard rat pellet diet was purchased from Amrut, Maharashtra, India

Preparation of High Carbohydrate Diet HCD):

The following ingredients were mixed with powdered NCD to form high carbohydrate diet (HCD) as described by Wolffram and Scharrer (22): casein 13%; carbohydrate 77% (starch 55%; sugar 22%); corn oil 4%; mineral mixture 5%; and vitamin mixture 2%.

Preparation of High Fat Diet (HFD):

High fat diet (HFD) was prepared by nixing powdered normal control rat diet (NCD) with 2% cholesterol dispersed in 6% heated corn oil (180^{o} for 15 min) as described by Kritchevsky et al. (23) as modified by Yusufi et al. (3).

Experimental Design

Adult male Wistar rats weighing 150-175 g body weight were stabilized on a standard rat pellet diet (Amrut Laboratories, Pune, India) and water ad libitum for one week before the start of the experiment. All animals were kept under conditions that prevented them from experiencing unnecessary pain according to the guide lines of Institution Ethical Committee and Ministry of Environment and Forests (CPCSEA), Government of India. Three groups of rats (9- 12 rats per group in each experiment) entered the study. Two groups of rats were then fed with a diet either rich in carbohydrate (HCD) or in fat (HFD) for 28 days. The third group of rats received standard rat pellet diet and water for the same period and used as Control. The animals were sacrificed on the same day under light ether anesthesia. The weights of the animals were recorded at the starting and completion of the experiment. Blood and urine were collected and the kidneys harvested and utilized for further analyses.

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Preparation of homogenates

After the completion of the experiment, the kidneys were removed, encapsulated and kept in ice-cold buffered saline (154 mM NaCl, 5 mM Tris-HEPES, pH 7.5). The cortex was carefully separated from medullary tissues as described earlier (13, 24). Since kidney demonstrates structural and functional heterogeneity, the studies were extended to observe the effect of HCD and HFD in whole cortex (WC) superficial cortex (SC) and juxtamedullary cortex (JMC) under same experimental conditions to delineate the site of their action. Kidney tissue homogenates (15% (w/v) were prepared in 0.1 M Tris-HCl buffer pH 7.5 using Potter-Elvehejem homogenizer (Remi motors, Mumbai, India) with five complete strokes. The homogenate was centrifuged at 3000g at 4˚C for 15 min to remove cell debris and the supernatant was saved in aliquots and stored at -20˚C for assaying various enzymes.

A 10% liver homogenate was similarly prepared in 10mM Tris-HCl buffer, pH 7.5. The homogenates were centrifuged at 2000g at 4˚C for 10 min to remove cell debris and the supernatant was saved in aliquots and stored at -20˚C for assaying the enzymes of carbohydrate metabolism, free-radical scavenging enzymes and for estimation of total-SH and lipid per oxidation as described by Farooq et al. (25) and Khan et al. (26).

Preparation of brush border membrane vesicles (BBMV) from various tissue zones of the kidney

BBMV were prepared from the homogenates of whole (BBMV-WC), superficial (BBMV-SC) and juxtamedullary (BBMV-JMC) cortex using the $MgCl_2$ precipitation method as previously described (7, 18, 19). Briefly, freshly minced tissues were homogenized in 50 mM mannitol and 5 mM Tris-HEPES buffer pH 7.0 (20 ml/g), in a glass Teflon homogenizer with 4 complete strokes. The homogenate was then subjected to high speed homogenization in an Ultra Turrex homogenizer (Type T-25, Janke & Kunkel GMBH & Co. KG. Staufen) for three strokes of 15 s each with an interval of 15 s. $MgCl_2$ was added to the homogenate to a final concentration of 10 mM and the mixture stirred for 20 min on ice. The homogenate was centrifuged at 2000g for 10 min in a Beckman centrifuge (J2 MI, Beckman instruments Inc, Palo Alto, C.A. USA) using JA-17 rotor and the supernatant was then recentrifuged at 35,000g for 30 min. The pellet was resuspended in 300 mM mannitol and 5mM Tris-HEPES, pH 7.4, with four passes by a loose fitting Dounce homogenizer (Wheaton IL, USA) and centrifuged at 35,000g for 20 min in a 15 ml corex tube. The outer white fluffy pellet of BBMV was resuspended in small volume of buffered 300 mM mannitol. Aliquots of homogenates and BBMV were saved and stored at -20˚C for BBM enzyme analyses. Each sample of BBMV was prepared by pooling tissues from 3-4 rats.

Serum chemistries

Serum samples were deproteinated by adding 3% trichloroacetic acid in a ratio 1: 3, left for 10 minutes and then centrifuged at 2000xg for 10 minutes. The protein free supernatant was used to determine inorganic phosphate and creatinine (7). The precipitate was used to quantitate total phospholipids. Blood Urea Nitrogen (BUN) and cholesterol levels were determined directly in serum samples. Glucose was estimated by o-toluidine method using kit from Span diagnostics (Mumbai, India). These parameters were determined by standard procedures as mentioned in a previous study (27).

Enzyme assays

The activities of BBM biomarkers enzymes, alkaline phosphatase (ALP), leucine amino peptidase (LAP), γ-glutamyl transferase (GGTase) in the homogenates and BBM preparations were determined as described earlier (24). The enzymes of carbohydrate metabolism, e.g., lactate dehydrogenase (LDH), malate dehydrogenase (MDH), glucose-6-phosphate (G6PDH) dehydrogenase and NADP-malic enzyme (ME), involved in oxidation of NADH or reduction of NADP were determined by measuring the extinction changes at 340 nm in a spectrophotometer (Cintra 5; GBC Scientific Equipment, Pty., Victoria Australia) as described elsewhere (27). The other enzymes, glucose-6-phosphatase and (G6Pase), fructose-1, 6-bisphospatase (FBPase) were determined as described in our previous studies (28). The activities of superoxide dismutase (SOD), catalase and glutathione peroxidase (GSH-Px) were determined as described by Priyamvada et al. (28). Lipid peroxidation (LPO) measured as MDA levels and total SH-groups were estimated as described earlier (28). Protein concentration was determined by the modified method of Lowry et al (29) as modified by Yusufi et al. (13).

Transport of ^{32}Pi

Measurement of ^{32}Pi (Bhabha Atomic Research Centre, India) uptake in freshly prepared BBMVs was carried out at 25 ˚C by rapid filtration technique as described by Yusufi et al. (13) either in the presence or absence of Na-gradient. Uptake was initiated by addition of 30 µl of incubation medium containing 100 mmol/l mannitol, NaCl/KCl 100 mmol/l, 5 mmol/l Tris–HEPES, pH 7.5, 0.1 mmol/l $K_2H^{32}PO_4$ to 15 µl BBM suspension (50–100µg protein) and incubated for the desired time intervals (see Results). The uptake was stopped by the addition of 3 ml ice-cold stop solution (containing 135 mmol/l NaCl, 5 mmol/l Tris–HEPES and 10mM sodium arsenate, pH 7.5) and filtered immediately through 0.45 µm DAWP Millipore (USA) filter and washed three times with the stop solution using a Cornwall-type syringe (Wheaton, IL). Correction for non-specific binding to filters was made by subtracting from all

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data the value of corresponding blank obtained by filtration of the incubation buffer without vesicles. The radioactivity of dried filters was measured by a liquid scintillation counter (Reckbeta, LKB, Wallace, Sweden) with 10 ml scintillation fluid (Cocktail T, SRL, India).

Statistical analyses

All data are expressed as Mean ± SEM for at least 4-5 different preparations. Statistical evaluation was conducted by one-way ANOVA and by unpaired student's t test using SPSS 7.5 software. A probability level of $p<0.05$ was selected as indicating statistical significance. All the changes were compared with control values for better understanding and clarity.

Results

Effect of High Carbohydrate Diet (HCD) and High Fat Diet (HFD) on Renal Tissues:

The present study describes the effect of high carbohydrate and high fat diets on (a) various serum and urine biochemical parameters, (b) the activities of BBM marker enzymes, (c) enzymes of cellular metabolism and, (d) transport functions of renal proximal tubular brush border membrane (BBM) isolated from rat renal whole cortex (WC), superficial cortex (SC) and Juxta-medullary cortex (JMC).

Effect of High Carbohydrate Diet (HCD) and High Fat Diet (HFD) on body weight and weight of the kidneys:

The effect of high carbohydrate (HCD) and high fat (HFD) diets was observed on the body and kidney weight of rats. As shown in Table 1, feeding HCD for 28 days, caused marked increase (+57%) whereas that of HFD caused a significant decrease (-30%) in the body weighs of the rats compared to control (NCD-fed) rats. The weight of the kidney however, was also changed in the same manner; increased (+30%) in HCD- and decreased (-29%) in HFD-fed rats.

Table 1. Effect of High Carbohydrate Diet (HCD) and High Fat Diet (HFD) on body weights and kidney weights of rats

Groups	Body weight (g)	Kidney weight (g)
Control	281 ± 14	1.47 ± 0.07
HCD	440 ± 20* (+57%)	1.91 ± 1.15* (+30%)
HFD	194 ± 08* (-30%)	1.05 ± 0.03* (-29%)

Results are mean ± SEM of eight different preparations.
Values in parenthesis represent percent change from control.
*Significantly different from corresponding control values at $p<0.05$ or higher degree of significance by independent *t* test and ANOVA

Effect of High Carbohydrate Diet (HCD) and High Fat Diet (HFD) on Serum and urine parameters:

The results (Table 2) showed that serum and urinary levels of creatinine were not affected by feeding of either HCD or HFD indicating a normal functioning of the kidney. However, serum inorganic Pi significantly increased in both HCD (+29%) and HFD (+27%) fed rats but urinary Pi was significantly lowered (-21%) in HCD and as well as in HFD (-28%) rats. Serum cholesterol (+12%) and phospholipids (+20%) were slightly increased in HCD rats whereas serum cholesterol (+27%) and phospholipids (+58%) profoundly increased in HFD rats (Table 2).

Effect of HCD and HFD on BBM marker enzymes in the homogenates and brush border membrane vesicles (BBMV) isolated from whole cortex (WC), superficial cortex (SC) and juxtamedullary cortex (JMC):

To determine the structural integrity, the effect of HCD and HFD was determined on the activities of ALkPase, and GGTase in the homogenates and BBM vesicles (BBMV) isolated from whole cortex (WC), superficial cortex (SC) and juxtamedullary cortex (JMC) (Table 3). The effect of HCD and HFD on the BBM enzyme activities were differentially observed in the homogenates and BBMV. In general, the activities of both ALkPase and GGTase were not changed significantly in HCD and HFD fed rats. However, the activity of ALkPase significantly increased in BBMV-WC (+18%), BBMV-SC (+40%) and BBMV-JMC (+20%) by HCD. And the increase in ALkPase activity was more marked in BBMV-SC compared to BBMV-JMC. In contrast, the activity of ALkPase was significantly decreased in BBMV-WC (-35%) in HFD rats as compared to control rats. A greater decline was, however, found in BBMV-SC (-41%) than BBMV-JMC (-19%). In contrast to ALkPase, the activity of GGTase was significantly lowered (-18%) in BBMV-WC in HCD fed as compared to controls rats (Table 3). Further analysis showed that GGTase activity was greatly declined in BBMV-JMC (-30%) than BBMV-SC (-12%). However, no significant effect of HCD was observed on GGTase activity in various homogenate preparations. As indicated in Table 3. the activity of GGTase was also decreased (-18%) in BBMV-WC in HFD fed rats. A greater decrease in GGTase activity was observed in BBMV-JMC (-38%) than BBMV-SC (-15%%). The activities in the homogenates was from WC, SC & JMC however not affected significantly.

Kinetic analyses indicate that the increase of ALkPase activity in BBMV-WC in HCD fed animals was largely due to the increase in both Vmax (+40%) and Km values (+19%). The effect of HCD on ALkPase greatly observed in BBMV-SC also due to increase of Vmax (+52%) and Km (+25%) values compared to BBMV-JMC (Vmax, +21%; Km, +11%)

The decrease of ALkPase by HFD feds was due to profound decrease in Vmax (-60%) and Km (-30%) values in BBMV-WC. The decrease of ALkPase by HFD was higher in BBMV-SC than in BBMV-JMC also due to marked decrease in Vmax and Km values more in BBMV-

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SC than in BBMV-JMC. The activity of GGTase was decreased by both HCD and HFD. Further analysis revealed that decrease in GGTase activity in BBMV-WC, BBMV-SC and BBMV-JMC in HCD rats was due to decrease in Vmax with small increase in Km values whereas the effect of HFD was due to decrease in both Vmax and Km values. The effect was more pronounced in BBMV-JMC than in BBMV-SC (Table 4).

Table 2. Effect of High Carbohydrate Diet (HCD) and High Fat Diet (HFD) on a) serum and b) urine parameters

Group/ Parameters	a) Serum					b) Urine	
	Creatinine (µmoles/ml)	Phosphate (µg/ml)	Glucose (mg/dl)	Phospholipids (µg/ml)	Cholesterol (mg/ml)	Creatinine (µmoles/ml)	Phosphate (µg/ml)
Control	25.62 ± 0.87	2.81 ± 0.2	63 ± 5	327 ± 11	3.08 ± 0.01	31.47 ± 0.68	1.52 ± 0.06
HCD	25.90 ± 1.15 (NS)	3.69 ± 0.4* (+29%)	127 ± 4* (+92%)	396 ± 22* (+20%)	3.55 ± 0.07* (+12%)	30.81 ± 0.77 (NS)	1.19 ± 0.05* (-21%)
HFD	26.61 ± 1.87 (NS)	3.59 ±0.2* (+28%)	135 ± 7* (+115%)	402 ± 7* (+23%)	4.90 ± 0.08* (+58%)	30.42 ± 0.80 (NS)	1.03 ± 0.08* (-28%)

Results are mean ± SEM of five different preparations.
Values in parenthesis represent percent change from control.
*Significantly different from corresponding control values at $p<0.05$ or higher degree of significance by independent *t* test and ANOVA

Table 3. Effect of High Carbohydrate Diet (HCD) and High Fat Diet (HFD) on the specific activities of (a) alkaline phosphatase (ALkPase) and (b) gamma glutamyl transpeptidase (GGTase) in cortical homogenates (CH) and brush border membrane vesicles (BBMV) from whole cortex (WC), superficial cortex (SC) and juxtamedullary cortex (JMC)

Group	WC		SC		JMC	
	CH	BBMV	CH	BBMV	CH	BBMV
a) ALkPase						
Control	31.80 ± 2.11	238.32 ± 5.58	20.71 ± 2.20	158.32 ± 4.49	15.14 ± 1.63	110.20 ± 2.20
HCD	35.18 ± 0.09 (+12%)	290.60 ± 1.39* (+18%)	25.30 ± 2.12* (+21%)	221.72 ± 2.07* (+40%)	15.24 ± 2.72 (NS)	132.53 ± 2.36* (+20%)
HFD	32.10 ± 2.11 (NS)	154.30 ± 1.50* (-35%)	17.50 ± 2.27* (-15%)	93.62 ± 3.20* (-41%)	15.10 ± 1.00 (NS)	89.30 ± 1.35* (-19%)
b) GGTase						
Control	40.58 ± 2.25	343.35 ± 3.25	22.50 ± 3.76	225.96 ± 9.45	59.45 ± 2.45	575.37 ± 7.96
HCD	38.43 ± 2.76 (NS)	292.07 ± 1.94* (-18%)	20.00 ± 0.02 (-13%)	198.35 ± 0.81* (-12%)	58.80 ± 1.40 (NS)	393.40 ± 0.60* (-30%)
HFD	37.34 ± 0.16 (-8%)	283.10 ± 2.18* (-18%)	20.47 ± 5.25 (-9%)	191.25 ± 9.50* (-15%)	50.37 ± 3.96* (-15%)	360.20 ± 7.45* (-38%)

Results are mean ± SEM of five different preparations. The activity of enzymes represents in (µmol/ mg protein/ h).
Values in parenthesis represent percent change from control.
*Significantly different from corresponding control values at $p<0.05$ or higher degree of significance by independent *t* test and ANOVA

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Table 4. Effect of High Carbohydrate Diet (HCD) and High Fat Diet (HFD) on kinetic parameters of a) Alkaline phosphatase (ALkPase) and b) gamma glutamyl transpeptidase (GGTase) in whole cortex (WC), superficial cortex (SC) and juxtamedullary cortex (JMC)

Group	BBMV-WC		BBMV-SC		BBMV-JMC	
	V_{max}	K_m x 10^{-3} M	V_{max}	K_m x 10^{-3} M	V_{max}	K_m x 10^{-3} M
a) ALkPase						
Control	166.66	0.285	125.0	1.05	83.33	0.54
HCD	232.95 (+40%)	0.347 (+19%)	190.23 (+52%)	1.315 (+25%)	101.50 (+21%)	0.60 (+11%)
HFD	66.66 (-60%)	0.200 (-30%)	66.60 (-47%)	0.64 (-38%)	62.50 (-25%)	0.42 (-22%)
b) GGTase						
Control	400.00	0.572	285.71	0.640	666.66	0.540
HCD	300.00 (-25%)	0.672 (+13%)	238.50 (-15%)	0.710 (+8%)	501.20 (-25%)	0.600 (+11%)
HFD	307.60 (-23%)	0.444 (-14%)	200.00 (-30%)	0.570 (-11%)	333.33 (-50%)	0.465 (-14%)

Results are mean of five different preparations.
Values in parenthesis represent percent change from control.
Km (Michaelis Menton constant) and Vmax (maximal velocity of enzyme reaction)

Effect of HCD and HFD on certain enzymes of carbohydrate metabolism in the homogenates obtained from whole cortex (WC-H), superficial cortex (SC-H) and juxtamedullary cortex (JMC-H)

To understand the metabolic activity of kidney, the effect of HCD and HFD, the activities of certain enzymes involved in carbohydrate metabolic pathways such as glycolysis, TCA cycle, HMP-shunt pathway and gluconeogenesis were determined in the homogenates of whole (WC-H), superficial (SC-H) and juxtamedullary (JMC-H) cortex. Feeding HCD significantly increased the activity of LDH (+42%), enzyme of glycolysis and MDH (+34%) enzyme of TCA cycle in WC-H. (Table 4). WC-H (+42%) and liver (+40%). Further analysis revealed that LDH activity markedly increased in JMC-H (+35%) than SC-H (+15%) whereas MDH activity showed higher increase in SC-H (+32%) than in JMC-H (+8%). In contrast, feeding of HFD decreased LDH (-33%) and MDH (-22%) activity in WC-H. The effect of HFD on LDH activity was found to be greater in JMC-H (-29%) and the effect on MDH activity was more pronounced in SC-H (-20%).

The activities of FBPase and G6Pase (gluconeogenic enzymes) were also determined. The activity of FBPase (-33%) and G6Pase (-22%) significantly decreased by HCD but FBPase (+21%) and G6Pase (+22%) activity increased by HFD in WC-H. The decrease of FBPase and G6Pase by HCD and increase of these enzymes by HFD were greater m SC-H, while the activities of the enzymes were not altered significantly m JMC-H by these diets (Table 5). The activities of G6PDH (an enzyme of HMP-shunt pathway) and ME (an enzyme of biosynthetic importance) which produce NADPH, were also determined in kidney tissues under the above two dietary conditions. The activities of these enzymes were significantly decreased by both HCD and HFD in all the tissues studied. The effect of HCD was more pronounced on G6PDH (-35%) activity than ME (-20%) activity whereas the effect of HFD was greater on ME (-40%) than G6PDH (-25%) in WC-H. The activity of G6PDH decreased to a greater extent in SC-H (-24%) than JMC-H (-15%) while the activity of ME appeared to be decreased more in JMCH (-16%) than SC-H (-12%) by HCD. The activity of G6PDH was decreased to greater extent in SC-H (-20%) than JMC-H (-15%) by HFD but ME activity decreased more in JMC-H (-28%) compared to SC-H (-14%) in response to HFD (Table 5).

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Table 5. Effect of High Carbohydrate Diet (HCD) and High Fat Diet (HFD) on the specific activities of **lactate dehydrogenase (LDH), malate dehydrogenase (MDH), fructose 1,6- bisphosphatase (FBPase), glucose-6-phosphatase (G6Pase), glucose-6-phosphate dehydrogenase (G6PDH) and malic enzyme (ME) in a) superficial cortical homogenate (SCH) and b) juxtamedullary cortical homogenate (JMCH)**

Enzymes Groups	LDH (µmol/mg protein/h)	MDH (µmol/mg protein/h)	FBPase (µmol/mg protein/h)	G6Pase (µmol/mg protein/h)	G6PDH (nmol/mg protein/h)	ME (nmol/mg protein/h)
a) WCH						
Control	95.57 ± 6.44	129.16 ± 3.28	12.65 ± 0.29	9.90 ± 0.40	814 ± 45	1050 ± 122
HCD	135.67 ± 5.76* (+42%)	175.20 ± 9.30* (+34%)	8.50 ± 0.48* (-33%)	7.72 ± 0.32* (-22%)	535 ± 40* (-35%)	836 ± 34* (-20%)
HFD	64.21 ± 5.42* (-33%)	101.30 ± 3.73* (-22%)	15.29 ± 0.25* (+21%)	11.99 ± 0.14* (+22%)	608 ± 30* (-25%)	629 ± 45* (-40%)
b) SCH						
Control	39.75 ± 6.35	75.95 ± 3.23	13.65 ± 0.28	8.15 ± 0.15	368 ± 7.2	426 ± 13
HCD	45.80 ± 5.95 (+15%)	101.80 ± 4.64* (+32%)	9.41 ± 0.36* (-31%)	6.60 ± 0.24* (-19%)	280 ± 5.0* (-24%)	375 ± 10* (-12%)
HFD	37.36 ± 6.09 (-6%)	60.76 ± 3.56* (-20%)	17.06 ± 0.59* (+25%)	9.37 ± 0.19* (+15%)	295 ± 6.3* (-20%)	366 ± 11* (-14%)
c) JMCH						
Control	65.95 ± 3.36	89.34 ± 3.54	6.23 ± 0.27	5.55 ± 0.27	475 ± 9.3	615 ± 10
HCD	89.03 ± 3.25* (+35%)	96.48 ± 5.25 (+8%)	5.92 ± 0.47 (-5%)	5.28 ± 0.36 (-5%)	403 ± 8.7* (-15%)	577 ± 12* (-16%)
HFD	46.82 ±2.95* (-29%)	83.97 ± 3.07 (-6%)	6.42 ± 0.19 (+3%)	5.68 ± 035 (+3%)	404 ± 10* (-15%)	443 ± 10* (-28%)

Results are mean ± SEM of five different preparations.
Values in parenthesis represent percent change from control.
*Significantly different from corresponding control at $p<0.05$ or higher degree of significance by independent *t* test and ANOVA.

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Effect of HCD and HFD on the transport of Pi by brush border membrane vesicles (BBMV) isolated from whole cortex (WC), superficial cortex (SC) and juxtamedullary cortex (JMC):

The effect of HCD and HFD was determined on the transport of Pi in BBMV isolated from whole cortex (BBMV-WC), superficial cortex (BBMV-SC) and juxtamedullary cortex (BBMV-JMC) in the presence and absence of Na-gradient (Nao>Nai) in early uphill phase (10 s, and 30 s) and after equilibration (120 min). As shown in Table 6, the transport of Pi in the presence of a Na-gradient (Nao > Nai) was markedly increased in the uphill phase, at 10 s (+38%) and 30 s (+50%) by HCD in BBMV-WC. The ^{32}Pi transport was also increased by HFD in the uphill phase at10s (+25%) and at 30s (+24%) in BBMV-WC but to a lesser extent than by HCD. However, the uptake of ^{32}Pi at equilibrium after 120 min was not changed either by HCD or HFD. The transport of Pi was also not affected when determined in the absence of a Na-gradient (NaCl was replaced by KCl in the incubation medium (data not shown). Kinetic analyses of Pi transport indicate that the uptake of Pi was markedly enhanced by HCD due to pronounced increase of both Vmax (+140%) and Km (+121.4%) values (Table 6). The increase in the uptake of Pi by HFD was also due to the increase in both Vmax (+48%) and Km (+44%) values. Further analysis showed that Na-gradient dependent uptake of Pi was also significantly increased BBMV-SC in the uphill phase at 10 s (+33%) and 30 S (+43%) by HCD but was not affected in BBMV-JMC. The uptake of Pi was similarly increased by HFD in BBMV-Sc and not altered in BBMV-JMC. The Na-independent uptake at 30s and at 120 man was not altered by HCD and HFD both m BBMV-SC and BBMV-JMC (data not shown). Kinetic analyses of Pi transport showed that the increase in Pi uptake in BBMV-SC by HCD and HFD was also due to the increase of Vmax and Km (Table 7). The changes in the kinetic parameters in BBMV-JM were rather small or not significant.

Effect of High Carbohydrate Diet (HCD) and High Fat Diet (HFD) on enzymatic and non-enzymatic antioxidant parameters in the homogenates of rat renal cortex and medulla:

It is well established that reactive oxygen species (ROS) generated by various environmental and nutritional factors are important mediators of cell injury and pathogenesis of various diseases especially in the kidney and other tissues (21,26,28, 30, 31). A major cellular defense against ROS is provided by GSH and redox cycle enzymes, e.g., superoxide dismutase (SOD), catalase. glutathione peroxidase (GSH-Px). To ascertain the role of antioxidant defense system, the effect of HCD and HFD was examined on enzymatic and non-enzymatic antioxidant parameters (Table 8). Feeding of HCD caused significant increase in lipid peroxidation (LPO) measured as the level of malondialdehyde (MDA), a known indicator of tissue injury in renal cortex (+20%) and medulla (+25%). The activity of SOD (-25%) and catalase (-23%) along with Total-SH (-38%) were decreased. However, GSH-Px activity was markedly increased (+41%) by HCD in renal cortex. The level of LPO (+25%) was also significantly increased by HCD in renal medulla but Total-SH accompanied by SOD (-30%) and catalase (-17%) activity were decreased. The activity of GSH-Px was not affected in renal medulla by HCD. In comparison to HCD, the level of LPO (+91%) was profoundly increased but Total-SH (-36%) and SOD activity markedly decreased (-32%) by HFD in the cortex. HDF caused a marked increase in LPO (+47%) along with significant decrease in Total-SH (-30%) and SOD (-21%) activity in the medulla. However, the activity of catalase and GSH-Px were not affected Table 8).

Table 6. Effect of High Carbohydrate Diet (HCD) and High Fat Diet (HFD) on Na-gradient uptake of ^{32}Pi in brush border membrane vesicles (BBMV) from whole cortex (WC), superficial cortex (SC) and juxtamedullary cortex (JMC)

	Na- gradient dependent transport of Pi (pmoles/mg protein)								
	BBMV-WC			BBMV-SC			BBMV-JMC		
	10 sec	30 sec	120 min	10 sec	30 sec	120 min	10 sec	30 sec	120min
Control	392 ± 20	762 ±38	276 ± 29	688 ± 30	1093 ± 46	191 ± 9.0	407 ±12	826 ± 4.6	175 ± 7.0
HCD	541 ±24* (+38%)	416 ±17* (+50%)	280 ±13 (NS)	915 ± 27* (+33%)	1568 ±31* (+43%)	193 ± 7.4 (NS)	439 ± 8 (+8%)	881 ± 5.8 (+7%)	177 ± 4.9 (NS)
HFD	491± 20* (+25%)	939 ± 11* (+24%)	292 ±21 (NS)	832 ± 15* (+21%)	1468 ±11* (+34%)	194 ±1.9 (NS)	446 ± 6.1* (+9%)	915 ± 40* (+11%)	174 ±2.3 (NS)

Results are mean ± SEM of five different preparations.
Values in parenthesis represent percent change from control.
*Significantly different from corresponding control values at p<0.05 or higher degree of significance by independent *t* test and ANOVA

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Table 7. Effect of High Carbohydrate Diet (HCD) and High Fat Diet (HFD) on kinetic parameters of Na-dependent ^{32}Pi uptake as a function of an external Pi concentration by brush border membrane vesicles (BBMV) from superficial cortex (SC) and juxtamedullary cortex (JMC)

Group	BBMV-WC		BBMV-SC		BBMV-JMC	
	Vmax	Km x 10^{-3} M	Vmax	Km x 10^{-3} M	Vmax	Km x 10^{-3} M
Control	1081	0.151	1600	0.131	870	0.114
HCD	2600 (+140%)	0.332 (+121%)	4000 (+159%)	0.277 (+111%)	1000 (+15%)	0.125 (+9%)
HFD	1600 (+48%)	0.217 (+44%)	2222 (+39%)	0.166 (+26)	1000 (+15%)	0.125 (+9%)

Results are mean of five different preparations.
Values in parenthesis represent percent change from control.
Km (Michaelis Menton constant) and Vmax (maximal velocity of enzyme reaction)

Table 8. Effect of High Carbohydrate Diet (HCD) and High Fat Diet (HFD) on non-enzymatic and enzymatic antioxidant parameters in the homogenate of rat renal Cortex and Medulla.

Tissues	LPO (nmoles/g tissue)	Total-SH (µmoles/g tissue)	SOD (Units/mg protein)	Catalase (µmoles/mg protein/min)	GSH-Px (µmoles/mg protein/min)
Cortex					
Control	103.6 ± 2.25	7.85 ± 0.45	14.28 ± 0.19	11.34 ± 0.72	0.093 ± 0.001
HCD	124.0±3.87* (+20%)	4.87 ± 0.23* (-38%)	10.77 ± 0.26* (-25%)	8.70 ± 0.20* (-23%)	0.131 ± 0.005* (+41%)
HFD	194.5 ±12.0* (+91%)	4.22 ± 0.38* (-36%)	9.40 ± 0.33* (-32%)	10.15 ±.0.10 (-11%)	0..100 ± 0.03 (+10%)
Medulla					
Control	72.17 ± 6.10	7.96 ± 0.36	21.90 ± 0.30	8.79 ± 0.24	0.077 ± 0.02
HCD	89.60 ± 5.70* (+25%)	5.91 ± 0.28* (-26%)	15.40 ± 0.21* (-30%)	7.26 ± 0.87* (-17%)	0.081 ± 0.002 (+5%)
HFD	106.00 ± 0.54* (+47%)	5.57 ± 2.23* (-30%)	17.25 ± 0.96* (-21%)	8.10 ± 0.25 (-9%)	0.080 ± 0.003 (+4%)

Results are mean ± SEM of eight different preparations.
Values in parenthesis represent percent change from control values.
*Significantly different from corresponding controls at $p<0.05$ or higher degree of significance by independent *t* test and ANOVA

Discussion

The present research was carried out to gain comprehensive knowledge regarding adaptive adjustment in rat kidney with dietary manipulations. The effect of HCD and HFD was determined on certain serum/urine parameters, the specific activities of various BBM enzymes, enzymes of metabolic pathways, transport of Pi and antioxidant parameters in the homogenates and BBMV preparations obtained from whole cortex (WC) superficial cortex (SC) and juxtamedullary cortex (JMC) in the same animals and under same experimental conditions to delineate the site of their action.

As described in the results, HCD fed rats gained in the body weight whereas HFD fed rats lost as copmared to control rats.. Serum and urine creatinine were not affected by both HCD and HFD, suggesting that the body adapts well and that normal kidney functions remained intact. Serum glucose, cholesterol and phospholipid were significantly increased by both HCD and HFD, indicating that the kidney adapted to maintain a positive level of these parameters that might be required for overall kidney functioning during nutritional stress caused by HCD and HFD. HCD induced increase in serum glucose might be due to glucose tolerance and hepatic insulin senstivity but the reason for increase in serum glucose by HFD is not clearly understood (2, 32). Since cholesterol and phospholipids are essential membrane components, their increased levels by HCD and HFD might have altered

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membrane fluidity that leads to changes in membrane reorganization affecting membrane enzymes and transport functions as reported earlier (17, 24, 27). The structural integrity as assessed by the status of BBM marker enzymes in the homogenates and BBMV preparations demonstrate that HCD and HFD differentially affected the activity of ALkPase and GGTase. ALkPase activity increased by HCD but decreased by HFD in BBMV-WC. However, GGTase activity was decreased by both HCD and HFD alike in BBM-WC. The increase by HCD and decrease by HFD in ALkPase activity was significantly higher in BBMV-SC than in BBMV-JMC. In contrast, decrease in GGTase activity by both HCD and HFD was much higher in BBMV-JMC. BBMV-SC and BBMV-JMC differs in enzyme distribution and enzyme activities as they are derived from different nephron populations located in different part of the cortex i.e. superficial (SC) and juxtamedullary (JMC) cortex (13). Kinetic studies revealed that changes in ALkPase activity in BBMV-SC and in GGTase activity in BBMV-JMC by both HCD and HFD were largely due to changes in Vmax values.

The renal handling of Pi is of paramount importance in the maintenance of Pi in the body. Pi is transported across the renal proximal tubular BBMV by Na-Pi co-transport system (13). BBMV-SC and BBMV-JMC exhibit diverse Na-Pi transport properties and BBM marker enzyme distributions (13) and respond differentially to fasting, hormones, drugs and diet (7, 16, 18, 19, 33-36). The present results show that Na-gradient dependent transport of Pi in uphill phase at 10s and 30s significantly increased by HCD and HFD in both BBMV-SC and BBMV-JMC albeit differentially. The effect was much greater by HCD than HFD. Kinetic analysis revealed that increase in Pi transport was due to profound increase of both Vmax and Km values by HCD in BBMV-SC than BBMV-JMC. HFD also increased Pi transport in BBMV-WC and also found to be more in BBMV-SC compared to BBMV-JMC as evident by the changes observed in Vmax and Km values. The observed increase in Vmax and Km values can be attributed to the increase in the number of Na-gradient-dependent Pi transporters and in part due to alterations in the intrinsic properties of the transporters as observed in many situations and reported earlier (16, 17, 37). Pi required for the production of metabolites and ATP in fact is conserved by the kidney. A direct relation between the transport of Pi and energy yielding metabolic reactions (glycolysis and TCA cycle) in various kidney tissues/zones has been demonstrated (7, 18, 19). It is imperative that any alterations to these pathways caused by nutritional stress or otherwise would determine the rate of renal transport functions (7, 18, 18, 27). As shown in the Results, the activities of certain enzymes in glycolysis, TCA cycle, gluconeogenesis, and HMP shunt pathway were differentially altered by HCD and HFD.

HCD caused significant increase of LDH (glycolysis) and MDH (TCA cycle) activities but the activities of FBPase, G6Pase (gluconeogenesis), G6PDH (HMP shunt) and ME markedly decreased in WCH. The effect of HCD was greater in superficial (SCH) compared to juxtamedullary cortex (JMCH) except LDH activity which was increased in JMCH than in SCH. In contrast, HFD significantly decreased the activity of LDH, MDH, G6PDH and ME but increased the activity of FBPase and G6Pase, the enzymes involved in gluconeogenesis in WCH. Except for LDH and ME activity, the activity of enzymes gluconeogenesis and HMP shunt the was greater in SCH compared with JMCH. Although the actual rates of the pathways were not determined, nevertheless, marked increase in LDH and MDH activity by HCD indicate that energy was being produced by oxidative metabolism via TCA cycle i by HCD in WCH and SCH whereas significant increase only in LDH activity without any change in MDH activity suggests a shift in energy production mainly by anaerobic glycolysis in JMCH. Due to high content of carbohydrates in the diet gluconeogenesis remained low. On contrast the results demonstrate that HFD decreased glucose degradation by but increased glucose production by gluconeogenesis from non-carbohydrate sources. The activities of G6PDH (HMP shunt) and NADP -malic enzyme (ME) which act to produce NADPH to support many reducing metabolic reactions and in maintaining high GSH levels required in anti-defense mechanism were decreased by both HCD and HFD.

A large body of evidences indicates that reactive oxygen species (ROS) and other free radicals are mediators of cell injury and inflammatory conditions. ROS, by-products of aerobic metabolism cause tissue injury and inflammation by several mechanisms including peroxidation of lipids, proteins and DNA [30]. Glutathione (GSH) and its redox cycle enzymes, e.g., SOD, catalase and GSH-Px neutralize ROS and prevent cellular damage. Studies on the effect of HCD and/or HFD on oxidative stress in the kidney are limited. Fasting has been shown to increase oxidative stress whereas calorie restricted diet was shown to reduce oxidative stress (6).

Recently, it has been reported that the rats fed HFD diet caused increase in kidney tissue MDA levels, and decrease in SOD, GSH, GSH-Px levels (39). In another study, fat and carbohydrate rich feed led to an increase in oxidative stress in rat kidney tissues led to nephrotoxicity, which in turn led to chronic kidney tissue damages (40). It was demonstrated that both HCD and HFD increased malondialdehyde (MDA) level whereas decreased GSH and the activities of SOD, catalase and GSH-Px in kidney tissues (40). Recently, we have reported that diets rich in carbohydrate

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(HCD) and fat (HFD) increased LPO (measured as MDA) and decreased enzymes of anti-oxidant defense mechanism in rat intestine and liver (21). Feeding of HCD and HFD caused marked but differential alterations in the enzymatic and non-enzymatic parameters of oxidative stress in rat renal cortex and medulla. HCD significantly increased LPO but decreased Total-SH and the activity of SOD and catalase in renal cortex. However, the activity of GSH-Px was remarkably increased. On the other hand, HFD caused profound increase in LPO (+91%) compared to HCD (+20%) in the cortex. The levels of Total-SH and SOD activity was significantly lowered but the activities of catalase and GSH-Px were not affected much by HFD in the cortex. Similar effects of HCD and HFD were observed in the medulla but they were relatively less pronounced. HCD and HFD induced decrease of anti-oxidant enzyme activities can be attributed to the decreased activities of G6PDH and ME which could produce enough NADPH required for anti-oxidant defense mechanism. The present study findings were consistent with the findings reported in other studies (39, 40).

In summary, the underlying mechanism by which HCD and HFD caused specific adaptive alterations in serum parameters, BBM enzyme activitties, BBM Pi transport, oxidative stress parameters and overall metabolic health appears to be complex. HCD and HFD differentially increased serum glucose, cholesterol and phospholipids. Serum inorganic phosphate (Pi) was increased but urine Pi decreased by both HCD and HFD. HCD increased enzymes of glycolysis and TCA cycle but decreased the enzymes of gluconeogenesis and HMP-shunt pathways in renal homogenates whereas HFD lowers the enzymes of glucose metabolism but increased enzymes of gluconeogenesis. The activity of BBM ALkPase was increased by HCD but decreased by HFD and GGTase activity was lowered by both HCD and HFD. The kidney was able to maintain a positive balance of serum Pi by increasing uptake of Pi by the BBMVs and decreasing Pi excretion in the urine. The BBM uptake of Pi was increased by HCD and HFD alike but the effect by HCD was greater than by HFD. Both HCD and HFD increased lipid peroxidation (MDA level) and decreased activity of superoxide dismutase and catalase in kidney tissues. We conclude that both high carbohydrate and high fat diet caused extensive kidney damage by disrupting renal energy metabolism, oxidant- antioxidant balance and transport functions.

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The authors declare that they have no conflict of interest.

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