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SERUM GLUTATHIONE PEROXIDASE AND PARAOXONASE-1 ENZYME ACTIVITIES IN CAMEL (*Camelus dromedarius*): EFFECT OF AGE AND SEX DIFFERENCES

N. Taha[1], S. Abou El-Noeman[2], M. Korshom[1], A. Mandour[1] and M. El-Feky[1]
[1]Department of Biochemistry, Faculty of Veterinary Medicine, Alexandria University, Alexandria, Egypt
[2]Department of Biochemistry, Faculty of Medicine, Tanta University, Tanta, Egypt

ABSTRACT

Camels are highly susceptible to oxidative stress due to style of breeding. The study was carried out on 41 clinically healthy camels. Serum lipid profile and malondialdehyde (MDA) levels were estimated by spectrophotometeric method. Serum glutathione peroxidase (GSH Px) enzyme activity was determined by method of Chiu *et al* (1976). The serum paraoxonase (PON-1) and arylesterase (ARE) activity was determined by the method of hydrolysis of paraoxon and phenyl acetate, respectively. The mean of paraoxonase and arylesterase activity in camel serum was the lowest in all ruminants tested until now. No sex difference between all tested parameters was found. Age had no significant effect on the serum concentration of cholesterol, triglyceride and LDL. The value of HDL-cholesterol of both male and female camels was higher in older animals compared to young animals and a 10 years old she camel showed less HDL serum level. The age had no effect on the level of serum level of MDA among male camel. However, female camel showed that the level of MDA gradually decreased by age up 10 years and then increased. This may be due to longer exposure of adult animals to pro-oxidants. The obtained data in the present study revealed that serum glutathione peroxidase activity was higher in female than males but this difference did not reach the level of significance and the activity of the enzyme is similar in young and adults camels. No age effect on the enzyme was detected. Serum PON-1 activity was significantly lower in one year old compared to 2 years old camel while PON-1 activity in 2 years old camels was similar to the enzyme activity in 5 years old camels in both sexes. However, PON-1 activity in 10 years old she camels was significantly lower than its activity in camels aged 2 years and 5 years. PON-1 activity correlated positively with the activity of arylesterase and serum levels of HDL but both enzymes correlated negatively with MDA.

Key words: HDL-cholesterol, oxidative stress, paraoxonase-1, triglyceride

Glutathione peroxidase (GSH Px, EC 1.11.1.9) constitutes the principal antioxidant defense system. It is selenoenzyme (an enzyme dependent on the micronutrient selenium) responsible for elimination of reactive oxygen species. It plays a critical role in the reduction of lipid and hydrogen peroxides. If GSH-Px activity is decreased, more hydrogen peroxide is present, which leads to direct tissue damage and activation of nuclear factor related inflammatory pathways. The other functions of GSH-Px, include detoxification of xenobiotics, modulation of redox-regulated signal transduction, regulation of cell proliferation, and immune responses. The enzyme activity is affected with many factors such as age, sex and nutrition Chiu *et al* (1976).

A large number of proteins that have antioxidant activity are known to be associated with lipoproteins and they are hypothesised to play key roles in protection from lipid oxidation and its consequences (Mackness *et al*, 1993). Among these, paraoxonase enzyme (PON, EC3.1.8.1) is a well-know enzyme associated specifically with HDL particles. Paraoxonase-1 is a calcium-dependent esterase synthesised in the liver that catalyses the hydrolysis of organophosphorous compounds (Aldridge, 1953). Paraoxonase gene family consists of 3 members PON-1, PON-2 and PON-3. Paraoxonase-1 is an antioxidant enzyme and it has arylesterase activity as it can catalyse the hydrolysis of phenyl acetate (an aryl ester) into phenol and acetate ® Anti-oxidative/ anti-inflammatory properities and activities of PON-1 provide a relief from physiological oxidative stress as well as toxic environmental chemicals (La Du *et al*, 1999).

SEND REPRINT REQUEST TO N. TAHA email: prof_nabil2006@yahoo.com

Camels have some biochemical, anatomical and physiological peculiarities which make them adapted to arid environment and poor feeding and drinking resources (Mousa *et al,* 2006). Camels are often subjected to conditions such as strenuous exercise, imbalanced nutrition and inhalation of chemicals or other stressful stimuli, this results in oxidative stress (OS). Although activity of GSH_Px and PON-1 in serum has already been confirmed in ruminants (Aldridge, 1953) and the first evidence on physical association of paraoxonase with lipoproteins was found in cattle by Kitchen *et al* (1973) and Don *et al* (1975). The status of serum glutathione peroxidase in camels has not been fully characterised. The present work was designed to investigate serum GSH_Px and PON-1 activity and their relation to lipid profile and MDA as index of lipid peroxidation in different age and sex of camels.

Materials and Methods

In present study 41 healthy Egyptian camels (*Camelus dromedarius*) were used and divided into 2 major groups. These camels had normal feed intake and faecal samples were negative for parasitic eggs.

Group 1 included 19 healthy male camels (5 one years old male camels, 5 two years old male camels and 9 five years old male camels) and Group 2 included 22 healthy she camels (5 one years old male camels, 4 two years old male camels, 6 five years old male camel and 7 ten years old she camels).

Collection of blood samples

At early morning, fasting blood samples (10 ml) were collected from jugular vein from all camels in clean dry labelled test tubes. The separated clear non haemolysed serum were collected in sterile clean Eppindorff tubes and stored at -20°C until analysis.

PON1 paraoxonase activity

PON1 activity towards paraoxon was determined according to the method described by Beltowaski *et al* (2002) by measuring the initial rate of substrate hydrolysis to p-nitrophenol, whose absorbance was monitored at 405 nm in the assay mixture (1 ml) containing 1.0 mM paraoxon, 1.0 mM $CaCl_2$ and 50 µl of serum in 100 mM Tris/HCl buffer (pH 8.0). The enzyme activity was calculated from extinction coefficient of p-nitrophenol (18290 M^{-1}. cm^{-1}) and was expressed in U/ml; where 1 U of enzyme hydrolyses 1 nmol of paraoxon/min.

PON1 arylesterase activity

PON1 activity toward phenylacetate was determined according to the method described by Beltowaski *et al* (2002) by measuring the initial rate of substrate hydrolysis to phenol, whose absorbance was monitored at 270 nm in the assay mixture (1.05 ml) containing 2mM substrate, 2mM $CaCl_2$ and 5 µl of serum in 100mM Tris/HCl (pH 8.0). The enzyme activity was calculated from extinction coefficient of phenol (1310 M^{-1}. cm^{-1}) and was expressed in U/ml; where 1U of enzyme hydrolyses 1µmol of phenylacetate/min.

Other biochemical parameters

The serum triacylglycerol, cholesterol and HDL-cholesterol were measured using commercial reagent kit from Biosystems Co, France. Lipid peroxides as malondialdehyde was assayed according to Placer *et al* (1966). Serum glutathione peroxidase activity (GSH-Px) was measured according to Chiu *et al* (1976).

Statistical analysis

Statistical analysis was performed using the SPSS 9.0 statistical software for Windows. The Scheffe test was used to calculate ANOVA, and the Pearson coefficient was used to calculate correlation. Statistical analysis was done by SAS (1996).

Results

The results of this work are presented in table 1,2,3,4 and 5. Table 1 showed the mean±standard deviation of the serum level of triacylglycerol, cholesterol lipoproteins, MDA, and activity of GSH Px and PON-1 in different age groups of dromedary camels. The data in table 2 represented effect of sex on tested parameters. No significant effect of sex could be noticed. In table 3, statistical difference ($P<0.05$) was observed in mean serum levels of HDL between males aged one year (35.76 ± 2.32mg/dl) and males aged 2 years (42.70 ± 2.32 mg/dl) and 5 years (50.41 ± 1.73 mg/dl). On other hand, the serum level of MDA showed a significant difference between different age groups of females ($P<0.05$). Females aged 2 years had high serum level of MDA (20.15 ± 1.83 nmol/ml) compared with females aged 5 years (12.93 ± 1.67 nmol/ml), then MDA level increased significantly in females aged 10 years (28.06 ± 1.55) which may be due to long exposure of environmental hazard. Younger males and females showed a statistical significant low activity of serum PON-1 compared with adult camels. Males aged 1 year (18.11± 1.74 U/ml) showed low activity of PON-1 compared with 2 years (27.13 ± 1.74 U/ml) and 5 years (28.58± 1.29 U/ml). Females aged one year (19.20 ± 1.96 U/ml) showed low activity of PON-1 compared with females aged 2 years (27.85 ± 2.19 U/ml) and 5 years (27.99 ± 1.79 U/ml). However,

at age 10 the activity of PON-1 decreased. In table 4 and 5 there is a significant (P<0. 05 and 0.001) positive correlation between PON-1 and arylesterase and HDL in both males and females On other hand there was a significant (P<0.05) negative correlation between PON-1 and arylesterase and MDA in both males and females.

Discussion

Our result revealed that the concentration of serum cholesterol and triacylglycerol was similar to the values reported by Al-Ali *et al* (1988), Osman and Al-Busadah (2003) and Al-Busadah (2007). In our study, the serum cholesterol concentration was lower than the values reported for other ruminant (Nazife *et al*, 2000). The concentrations of HDL and LDL in the serum of camels were similar to those reported previously but lower than the value reported for other ruminant (Osman and Al-Busadah, 2003). Large species differences in lipoproteins profiles and the percentage of total cholesterol and triglycerides carried by each lipoprotein class were recorded in different animals whereas in human and pigs, the majority of cholesterol is transported as LDL, in cattle cholesterol is equally divided between LDL and HDL, while in sheep and horses, the majority of cholesterol circulates as HDL (Latimer *et al*, 2003). In the camel, the majority of cholesterol circulates as LDL, which apparently has more cholesterol and less triglyceride, and HDL has almost equal amounts of cholesterol and triglyceride. As regard lipid profile no sex difference was found among male and female camels. Age had no significant changes on the serum concentration of cholesterol, triglyceride, and LDL. However, the value of HDL-cholesterol of both male and female camels was higher in older animals as compared to young animal and 10 years old she camel showed less HDL serum level. Noro *et al* (1993) found a high concentration of LDL and a low concentration of HDL in calves immediately after birth, by 6 days of age, the LDL concentration had decreased and the HDL concentration had increased to the levels found in adolescent animals. Noguchi (1993) reported that, in humans, the concentrations of LDL and VLDL increased and the concentration of HDL decreased with increasing age. Hugi and Blum (1997) reported that in calves the concentration of cholesterol increased transiently with age, but triglycerides did not show a consistent change. The discrepancy between results may be due to environmental and nutritional factors.

MDA serum level is greater than that reported by Amoli *et al* (2009) and less than that of Mohamed (2007). No sex difference was existed between male and female camels. The age had no effect on the level of serum level of MDA among male camel. However, female camel showed that the level of MDA gradually decreased by age 10 years then increased. This may be due to longer exposure of adult animals to pro-oxidants as manifested by the higher levels of lipid peroxides in adult animals when compared with young animals. Older camels with one hump has more fat content than young camel which may increase the lipid peroxidation (Kadim *et al*, 2002).

Glutathione peroxidase (GSHPx) plays a critical role in the reduction of lipid and hydrogen peroxides. GSHPx activity in erythrocytes and whole blood was determined by many other authors and the activity of enzyme varied from erythrocytes and whole blood. The activity of erythrocytes GSHPx ranged from 60-400 U/g Hb according to age and sex of the camel.

Table 1. Mean and standard deviation of serum lipid profile, malondialdehyde, antioxidant enzymes activity of healthy camels.

Parameter	N=41 camel
Triacylglycerol (mg/dl)	93.36 ± 2.50
Total cholesterol (mg/dl)	97.91 ±3.1 1
High density lipoprotein (mg/dl)	43.53 ±7.83
Low density lipoprotein (mg/dl)	34.64 ±5.55
Malondialdehyde level (nmol/ml)	17.19 ± 1.3 3
Glutathione peroxidase activity (U/ml)	1.77 ± 0.08
PON1 paraoxonase activity (U/ml)	25.42 ± 1.33
Arylesterase (U/ml)	11.78±0.23

Table 2. Effect of sex differences on serum paraoxonase1 (Paraoxonase and Arylesterase activities), glutathione peroxidase activities and malondialdehyde, Triacylglycerol, Total cholesterol, High density lipoprotein and Low density lipoprotein level (Data are expressed in Mean ±SD).

Parameter	Male camel N= 19	She camel N=22
Triacylglycerol (mg/dl)	90.36 ± 3.04^{A}	96.31 ± 2.26^{A}
Total cholesterol (mg/dl)	95.91 ± 2.71^{A}	98.45 ± 3.42^{A}
High density lipoprotein (mg/dl)	44.53 ± 1.83^{A}	43.65 ± 1.99^{A}
Low density lipoprotein (mg/dl)	33.64 ± 2.55^{A}	35.11 ± 3.21^{A}
Malondialdehyde level (nmol/ml)	18.19 ± 1.43^{A}	16.74 ± 1.23^{A}
Glutathione peroxidase activity (U/ml)	1.68 ± 0.05^{A}	1.86 ± 0.11^{A}
PON1paraoxonase activity (U/ml)	25.42 ± 1.33^{A}	25.02 ± 1.32^{A}
Arylesterase (U/ml)	11.93±0.23^{A}	11.78±0.36^{A}

No significant difference was found at P> 0.05.

Table 3. Effect of age differences on serum paraoxonase-1 (paraoxonase and arylesterase activities), glutathione peroxidase activities and malondialdehyde, triacylglycerol, total cholesterol, high density lipoprotein and low density lipoprotein level (data are expressed in Mean±SD).

Parameter	Male camel			She camel			
	1 yearN =5	2 yearN =5	5 yearN =9	1 yearN =5	2 yearN =4	5 yearN =6	10 yearN =7
Triacylglycerol (mg/dl)	83.70±5.98^{A}	91.52±5.98^{A}	93.42±4.46^{A}	97.26±5.07^{A}	100.90±6.37^{A}	92.45±5.20^{A}	93.61±4.82^{A}
Total cholesterol (mg/dl)	91.12±5.43^{A}	97.00±5.43^{A}	97.98±4.05^{A}	91.10±6.26^{A}	106.60±7.00^{A}	99.13±5.71^{A}	98.66±5.29^{A}
High density lipoprotein (mg/dl)	35.76±2.32^{C}	42.70±2.32^{B}	50.41±1.73^{A}	39.96±3.63^{A}	45.62±4.06^{A}	45.42±3.31^{A}	42.67±3.07^{A}
Low density lipoprotein (mg/dl)	37.06±4.89^{A}	38.01±4.89^{A}	29.31±3.64^{A}	31.70±5.90^{A}	40.82±6.95^{A}	34.14±5.38^{A}	37.26±4.98^{A}
Malondialdehyde (nmol/ml)	21.32±2.74^{A}	19.22±2.74^{A}	15.87±2.04^{A}	20.15±1.83^{B}	18.20±2.05^{BC}	12.93±1.67^{C}	28.06±1.55^{A}
Glutathione peroxidase (U/ml)	1.61±0.11^{A}	1.69±0.11^{A}	1.72±0.08^{A}	1.77±0.19^{A}	1.83±0.22^{A}	1.96±0.18^{A}	2.11±0.16^{A}
PON1 paraoxonase activity (U/ml)	18.11±1.74^{B}	27.13±1.74^{A}	28.58±1.29^{A}	19.20±1.96^{B}	27.85±2.19^{A}	27.99±1.79^{A}	21.42±1.66^{B}
PON1 arylesterase activity (U/ml)	11.59±0.44^{A}	11.82±0.44^{A}	12.18±0.33^{A}	10.90±0.58^{A}	11.64±0.65^{A}	12.59±0.53^{A}	11.46±0.62^{A}

Means within the same row carrying different letters are significantly different (P£ 0.05).

However, the work on serum or plasma GSHPx activity is scanty. The activity of serum GSHPx was close to those previously reported by Corbera *et al* (2001). Furthermore, the results of present study showed that the activity of GSHPx is low in the camel compared to human, sheep and cattle. Serum glutathione peroxidase activity was higher in female than males but this difference did not reach the level of significance and the activity of the enzyme is similar in young and adults camels. Female have higher GSHPx activity than males. The increased activity of enzyme in female could be attributed to the higher metabolic selenium requirements in the males than females. Mousa *et al* (2006) showed that GSH-Px activity was higher in adult camels than in the young. In contrary, Hamliri *et al* (1990) did not find age or sex affecting the activity of GSH_Px. In human, the GSHPx activity declined by age.

Present study revealed that camel serum exhibits the low serum PON-1 paraoxonase and arylesterase activities as compared to other ruminants. The cause of low activity of serum PON-1 and arylesterase is not known. The low PON-1 activity may be contributed to several factors such as environmental factors e.g. subjecting camel to oxidative stresses due to style of breeding and type of feeding. Dalgard (2008) reported that diets, foods or food components modulate PON1 activity and concentration. The camel has high body mass index compared to other animals. This BMI exposed to wide scale of environmental stress (more oxidative stress than other animals) inhibited the PON-1 activity.

Biochemical factor well seen in large species as differences in lipoproteins profiles and the percentage of total cholesterol and triglycerides carried by each lipoprotein class HDL-cholesterol and tobacco smoking may contribute to the modulation of PON-1 activity (Ferre *et al*, 2003). Therefore, lower PON-1 and arylesterase activity may be species specific. The concentration of HDL (the enzyme is associated with its own N-terminal domain to phospholipids of HDL sub fraction) in the serum of camel was lower than the values reported for other ruminants (Mohamed *et al*, 2008). Consequently, the serum PON-1 content and activity was less in camel other than ruminants.

Ferre *et al* (2003) indicated that the variability of serum paraoxonase activity is regulated mainly by genetic determinants. It has been suggested that the genetic polymorphism of PON-1 play similar role in the camel. There was a high correlation (P< 0.01) between paraoxonase activity and arylesterase activity of paraoxonase-1. These results were in accordance with that of Miyamoto *et al* (2005) who reported that in bovine serum, there was a high correlation between paraoxonase activity and arylesterase activity and between paraoxonase activity and the amount of PON1 judged by immunoblotting.

There was no significant difference in serum PON1 arylesterase activity between both sexes. Hashim and Zarina (2007) concluded that there was non significant difference in PON1 activity between male and female human among control and diabetic ones. Tomas *et al* (2000) noticed that PON1 activity in normocholesterolemic humans was unaffected by sex.

Table 4. Correlation of PON1 paraoxonase activity with different parameters in male and she camels.

Parameter	r_1	r_2
Arylesterase activity	0.719 **	0.685**
Triacylglycerol	0.130	0.065
Total cholesterol	0.272	0.546
High density lipoprotein	0.719**	0.676**
Malondialdehyde level	- 0.575 *	-0.655**
Glutathione peroxidase activity	0.313	0.027

Table 5. Correlation of PON1 arylesterase activity with different parameters in male and she camels.

Parameter	r_1	r_2
Triacylglycerol	- 0.086	- 0.191
Total cholesterol	- 0.015	0.504
High density lipoprotein	0.389*	0.723**
Malondialdehyde level	- 0.511*	- 0.594 *
Glutathione peroxidase activity	0.290	0.135

r_1 correlations in male camels. * Significant at (P< 0.05).
r_2 correlations in she camels. ** Significant at (P< 0.01).

In contrast to camel and human, Wehner *et al* (1987) studied serum PON1 activity in different strains of mice and reported that female animals had a 14-26% higher activity than males. Ali *et al* (2003) reported that hepatic PON1 mRNA levels in female mice were 40% higher than in males.

Serum PON1 paraoxonase and arylesterase activities was significantly lower in 1 year old camel in both male and female than in 2 year old camels but the PON1 activity in 2 year old camels was similar to its activity in 5 year old camels in both sexes. Li *et al* (1997) and Moser *et al* (1998) reported that rat serum and liver PON1 activity was very low at birth and increased upto postnatal day 21, with parallel increase in liver mRNA. A recent study in human has shown that serum PON1 activity is very low at birth and increases over time, reaching a plateau between 6 and 15 months of age (Cole *et al*, 2003). In rats, PON1 activity is quite constant over time, once it reaches adult values, no differences were found in plasma and liver PON1 activity between 3- and 24-month-old animals (Karanth and Pope, 2000). Low PON1 activity during development could represent a relevant risk factor for increase susceptibility to the toxicity of certain organophosphorus insecticides, as indicated by several animal studies (Moser *et al*, 1998). Significant decrease of PON1 paraoxonase and arylesterase activities in 10 year old she camels than its activity in 5 year old she camels were also seen in recent investigations that have reported a progressive decrease in PON1 activity in elderly subjects (Milochevitch and Khalil, 2001 and Jarvik *et al*, 2002). This decline in PON1 activity may be related to the development of oxidative stress conditions with ageing, and would have an impact on the increased incidence of atherosclerosis with age (Senti *et al*, 2001). Seres *et al* (2004) showed that HDL from elderly subjects was more susceptible to oxidation than HDL from young subjects measured by higher lipid peroxidation rate. The decrease in PON1 activity could be related to the development of oxidative stress conditions with ageing and the increased HDL susceptibility to oxidation in elderly subjects.

As PON1 exists in serum exclusively as a component of HDL that protects both HDL and LDL, against oxidation, the results of the present work established a significant positive correlation of both paraoxonase and arylesterase activities of serum paraoxonase1 with HDL-cholesterol levels. These results are in agreement with results previously reported by Ferré *et al* (2003), which confirmed the correlation between PON1 activity and HDL levels, and showed that HDL-cholesterol is a significant predictor of PON1 activity where 1 mmol/L increase in HDL-cholesterol was associated with a mean increase in serum PON1 activity of 53.5 U/L. This association was also reported by Jarvik *et al* (2002) and Amany (2009) and seems logical because PON1 circulates in plasma linked to this lipoprotein. In contrast, a pervious study by Turk *et al* (2005) revealed that a significantly lower PON1 activity in cows with hepatomegaly without decreasing the HDL- cholesterol concentration indicates that the PON1 activity can decrease independently of the HDL- cholesterol concentration.

There was significant negative correlation between PON1 activity and MDA levels in both male and she camels groups. Sarandol *et al* (2005) and Hashim and Zarina (2007) reported a significant negative correlation (P<0.01) between PON1 activity and plasma MDA levels in the human. The explanation of cause of negative correlation based on that an increased lipid peroxidation may reduce serum PON1 activity, because PON1 hydrolyses lipid peroxides formed on lipoprotein, leading to exhaustion of the enzyme activity. Turk *et al* (2008) reported that the correlation between PON1 activity and MDA level was non significant in dairy cows. No correlation was found between PON-1 and arylesterase and GSHPx. In conclusion, serum paraoxonase-1 activity and arylesterase in camel was the lowest in all ruminant tested till now. However,

there was a high correlation (P< 0.01) between the 2 enzyme activities. Moreover, serum paraoxonase-1 activity was not markedly affected by sex differences but it was significantly affected by age differences.

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