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EFFECT OF PROSTAGLANDIN E2 (PGE_2) ON CARBOHYDRATE METABOLISM IN NORMOTENSIVE AND INDUCED HYPERTENSIVE RATS

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SUMMARY

The present study was conducted to investigate the effect of the vasodilator PGE2 on carbohydrate metabolism in both of normotensive and hypertensive adult male rats.

PGE2 was injected intraperitoneally in a dose of 40µg/kg body weight per day to normotensive and hypertensive groups for 8, 16, and 24 days. Hypertension was induced in normal rats by administeration one subcutaneous injection of an aqueous suspension of 25-mg/kg-body weight of deoxycorticosterone acetate (DOCA) per week. Moreover, a saline solution was given to rats to drink during the 4-weeks of hypertension induction periods.

PGE2 caused significant glycogenolytic effect with a corresponding hyperglycemia after 16 and 24 days of treatment in normotensives and hypertensives. However, Glucose-6-phosphatase exhibited insignificant increase through out the experimental peroids. Lactate levels in serum increased insignificantly, but the increase reached significant value after 24 days of treatment in normotensive animals. Activity of lactate dehydrogenase in serum and liver did not change significantly after injecting PGE2 at any time interval. Long term administration of low doses of PGE2 caused significant increases in serum glucose with corresponding declines in liver glycogen levels in both of normotensive and hypertensive rats.

INTRODUCTION

Hypertension is frequently associated with insulin resistance (Ferrannini et al., 1987 and Cíia et al., 1999). It was assumed that there is a close correlation between circulating insulin level and systemic blood pressure. This correlation may be mediated by the inhibitory effect of insulin on production of vasodilation inducing prostaglandins, e.g., PGE2 and PGI2 by adipose tissue (Axelrod, 1991 and Chatzipanteli et al., 1996). Furthermore, prostaglandins of the E type have been demonstrated to inhibit insulin secretion in vivo (Roberston et al., 1979 and Villar et al., 1987).

The role of prostaglandins E in the regulation of carbohydrate metabolism has been discussed controversially in previous studies. For example, hyperglycemic effect of PGE2 was observed in healthy subjects (El-Lamie, 1978 and Villar et al., 1987) whereas results obtained by by Eklund and Carlson (1980) and Shigihara (1994) failed to document any change in serum glucose after intravenous infusion of PGE1 or PGE2 in humans. While, Mine et al., (1990) concluded that PGE2 stimulated glycogenolysis in isolated rat hepatocytes, but Okumura and Saito (1990) and Okumura et al., (1993) reported that PGE2 and dimethyl PGE2 stimulated the incorporation of glucose into glycogen in rat hepatocytes in primary culture.

The present study was conducted to clarify the effect of the vasodilator PGE2 on carbohydrate metabolism in both normotensive and DOCA induced hypertensive rats. The tested parameters were: serum glucose, lactates, lactate dehydrogenase in serum and liver, liver glycogen and glucose-6-phosphatase.

MATERIALS AND METHODS

Male rats (Sprague-Dawley) weighing 100-120g were used in the present study. Animals were kept at well aerated cages with acess to the standard laboratory diet and water ad libitum. Seventy two rats were divided into two main groups: normotensive and induced-hypertensive groups. Each of these main groups was subdivided into two groups of 18 rats each as follows:

1. Normotensive Group:

a) Control Group: Rats were injected with PGE2 vehicle (0.1% ethanol in saline) for 8,16 or 24 days.

b) Treated Group: Rats were injected with PGE2 for 8,16 or 24 days.

2. Hypertensive Group:

a) Control Group: Rats were treated with DOCA and salt for 4 weeks, then PGE2 vehicle was injected for 8,16 or 24 days.

b) Treated Group: Rats were treated with DOCA and salt for 4 weeks, followed by injection with PGE2 for 8,16 or 24 days.

Induction of Hypertension:

Hypertension was induced in normal rats by ad-

ministering one subcutaneous injection per week of an aqueous suspension of 25mg/kg-body weight DOCA (Sigma Chemical Co.). The dose of DOCA was determined as described by Reid et al., (1975) and Ali et al., (1993). During the 4-weeks hypertension induction period the rats were given a saline solution (1% NaCl in water) to drink ad libitum. The DOCA injections and salt drinking water were discontinued after 4 weeks and tap drinking water was used instead.

Dosage and Administration of PGE2:

Prostaglandin E2 (PGE2) was obtained from Sigma Chemical Co., in a crystalline form. The solution of injection was prepared in aqueous solution containing 0.1 ml absolute ethanol for each mg of prostaglandin, then stored at -20°C and diluted daily with saline before use (Hassan, 1979 and Hayashi, 1992). PGE2 was administered intraperitoneally in a dose of (40g/kg body weight (Al-Azhary, 1988) in 0.1 percent ethanol per day for 8,16 or 24 days. Control groups were injected with the same percentage of ethanol alone. The administration of PGE2 into hypertensive rats started after stopping salt- DOCA treatment at the end of the fourth week.

At the end of each time interval, rats in each subgroup were decapitated and blood samples were collected from each rat into a clean centrifuge tube. Serum was separated and kept at-20°C for biochemical analysis. Immediately after sacrifice, liver was rapidly excised, dissected then stored at -20°C till analysis.

Biochemical Analysis:

Serum glucose was determined according to the method of Trinder, (1969) using Labkit Kit. The colorimetric method described by Trinder, (1972) was followed for determination of serum lactate using Labkit Kit. Lactate Dehydrogenase (LDH) enzyme activity was measured according to Allain (1973) using Teco Kit. Liver glycogen was determined by the one method described by Carroll et al., (1956). Glucose-6-phosphatase activity was determined according to the method of Swanson and Marjorie (1950).

Statistical Analysis:

The results were expressed as means ± standard error. ìtî test was done to show the significance between two independent means was used according to the method of Dawson-Saunders and Trapp (1994).The percentage of change of each parameter from control value was calculated.

RESULT

As shown in Table 1, administration of PGE2 resulted in increases of serum glucose levels all over the experimental period. This increase reaches significant ($p<0.05$) value of 13.9%, and highly significant value of 21.44% after 24 days in hypertensive and normotensive groups, respectively, versus their controls.

Table (1) Effect of daily intraperitoneal administration of PGE2 (40µg/kg b.wt.) on glucose and lactate (mg/dl) in serum of normotensive and DOCA (25mg/kg b.wt)- salt hypertensive male rats at different time intervals.

Parameters		After 8 days		After 16 days		After 24 days	
		Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
Glucose (mg/dl)	Control	91.53±2.54	97.73±3.21	96.08±5.57	98.74±5.96	93.60±3.47	99.54±2.65
	Treated	95.80±2.20	103.02±4.23	106.25±3.64	110.65±5.20	113.67±3.94**	113.38±4.26*
	% of change	4.7%	5.4%	10.58%	12.06%	21.44%	13.90%
Lactate (mg/dl)	Control	25.42±0.98	29.49±1.14	22.71±0.73	28.87±0.79	24.47±1.03	29.15±1.12
	Treated	27.69±0.73	32.08±0.92	24.69±0.92	31.34±0.91	28.07±0.94*	32.68±1.39
	% of change	8.93%	8.78%	8.72%	8.56%	14.71%	12.11%

Data are expressed as means ± standard error (S.E.). Number of animals = 6 per each group
* Significant change at $P < 0.05$. ** Highly significant change at $P < 0.01$

Table (2) Effect of daily intraperitoneal administration of PGE2 (40µg/kg b.wt.) on concentration of lactate dehydrogenase (LDH) in serum (IU/L) and liver (IU/g. wt. tissue of normotensive and DOCA (25mg/kg b.wt)- salt hypertensive male rats at different time intervals.

Parameters		After 8 days		After 16 days		After 24 days	
		Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
Concentration of serum LDH (IU/L)	Control	245.49±7.17	251.24±7.13	254.02±8.60	260.68±7.28	254.55±8.30	264.11±6.88
	Treated	255.23±11.4	256.68±7.28	259.94±12.70	264.06±8.73	255.64±9.30	260.99±7.03
	% of change	3.97%	2.17%	2.33%	1.30%	0.43%	-1.18%
Concentration of liver LDH (IU/g. wt tssue)	Control	89.7±1.71	89.22±0.96	84.24±1.02	86.88±1.68	88.20±1.11	75.39±2.10
	Treated	90.75±1.59	88.57±0.78	83.28±1.14	86.73±2.67	85.74±1.59	75.59±1.89
	% of change	1.17%	-0.73%	-1.14%	-0.17%	-2.79%	0.27%

Data are expressed as means ± standard error Number of animals = 6 per each group

Table (3) Effect of daily intraperitoneal administration of PGE2 (40μg/kg b.wt.) on liver glycogen (mg/g. wt tissue) and activity of liver glucose-6-phosphatase (μmol-Pi. min/g. wt. tissue) in normotensive and DOCA (25mg/kg b.wt)- salt hypertensive male rats at different time intervals.

Parameters		After 8 days		After 16 days		After 24 days	
		Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
Liver glycogen (mg/g. wt. tissue)	Control	11.10±0.51	11.56±0.43	10.54±0.62	11.31±0.63	11.10±0.54	12.20±0.59
	Treated	9.93±043	10.38±0.56	8.63±0.53*	9.57±0.44*	9.24±0.53*	10.34±0.48*
	% of change	-10.54%	-10.21%	-18.12%	-15.38%	-16.76%	-15.25%
Glucose-6-phosphatase (μmol. Pi.min/ g. wt. tissue)	Control	2.22±0.10	2.39±0.19	2.05±0.16	2.13±0.19	2.21±0.10	2.29±0.19
	Treated	2.40±0.11	2.43±0.15	2.13±0.20	2.24±0.12	2.37±0.12	2.45±0.13
	% of change	8.11%	1.67%	3.90%	5.16%	7.24%	6.99%

Data are expressed as means ± standard error (S.E). Number of animals = 6 per each group
* Significant change at $P < 0.05$.

Serum lactate levels exhibited insignificant increases after injecting PGE2 into normotensive and hypertensive groups (Table 1). The only significant increase was noticed in normotensive rats at 24 days of treatment versus their control.

Data obtained in Table 2 showed that the alterations in both of serum and liver LDH activity seemed to be not change after PGE2 administration.

PGE2 administration induced decreases in hepatic glycogen content that were significantly ($p<0.05$) lower than their respective controls at 16 and 24 days in both of normotensive and hypertensive groups (Table 3). The percentage of decreases after 16 and 24 days were nearly in the same range.

The action of PGE2 administration induced slight changes in liver glucose-6-phosphatase (Table 3). Such changes were manifested by insignificant increases ($p>0.05$) through out the experimental periods.

DISCUSSION

The present study showed that administration of PGE2 caused significant declines in hepatic glycogen content after 16 and 24 days in both normotensives and hypertensives. The results coincide with that obtained by May (1973) who observed glycogenolytic effects of PGE1 on the liver in

mice and rat Furthermore, the glycogenolytic effect of PGE2 was observed in hepatocyte cell culture. Such effect was attributed to EP1 receptor that stimulate glycogenolysis via inositol triphosphate - linked signal chain which leads to increased glycogen phosphorylase activity (Mine et al., 1990 and Puschel et al., 1993).

With regard to liver glucose-6-phosphatase activity, PGE2 did not induce significant alteration throughout the experiment periods.

Administration of PGE2 led to marked increases in serum glucose especially after 24 days. These changes are generally parallel to those occurred in liver glycogen content during the different experimental periods. Such hyperglycemic effect of PGE2 is consistent with the results of Villar et al., (1987) who observed marked increase in plasma glucose after intra-arterial administration of PGE2. Moreover, May (1973) using PGE1, reported that significant increases in serum glucose occurred after intraperitoneal infusion into mice and rats. In human, El-Lamie, (1978) reported that intravenous infusion of PGE2 produced a significant hyperglycemic effect in normal groups, but no added significant rise in blood glucose was noticed in diabetic groups. In contrast, other studies carried out by Eklund and Carlson (1980) and Shigihara (1994) failed to document any change in serum glucose after intravenous infusion of PGE1 or PGE2 in humans. Kasim et al., (1992) concluded that PGE1 analogue (enisoprost) caused a reduction in fasting serum glucose during the fourth week of treatment in diabetic subjects, but the change was transient, returning to the baseline values despite continuation of enisoprost therapy. The hyperglycemic effect of PGE2 may be due to direct glycogenolytic effect of E-prostaglandins, or reflexly by the increased secretion of catecholamines secondary to the hypotensive action of PGE2 (May, 1973 and El-Lamie, 1978). Furthermore, PGE2 could decrease plasma insulin, with a corresponding marked increase in plasma glucose (Villar, et al., 1987). Similarly, Borrisova et al., (1991) reported that PGE2 decreased plasma C-peptide level and insulin receptor affinity in man, and thus it reduced the peripheral glucose utilization.

Serum lactate levels exhibit insignificant effect after giving PGE2 into rats, but increases reach significantly after 24 days in normotensive group. However, previous results did not report any significant changes in serum lactate after PGE1 or PGE2 treatment to humans (Eklund and Carlson, 1980 and Shigihara, 1994).

PGE2 injection did not affect lactate dehydrogenase activity in serum or in liver of rats. This finding is consistent with Hayashi (1992) who reported that neither PGE2 nor indomethacin affect-

ed LDH activity in normal mice.

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