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EXPERIMENTAL STUDY

Protective effect of vitamin B5 (dexpanthenol) on cardiovascular damage induced by streptozocin in rats

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Abstract: *Objectives:* This study investigated whether Dexpanthenol (DEX) improves diabetic cardiovascular function and cardiac performance by regulating total oxidant and antioxidant status.
Methods: Diabetes was induced by a single intraperitoneal injection of Streptozocin (50 mg/kg in 1 ml of saline) and treatment groups received DEX (300 mg/kg/day) for 6 weeks. Endothelium (in)dependent relaxation responses were assessed in thoracic aortic rings and coronary vasculature together with alpha receptor and voltage dependant contractile responses of aorta. Myocardial contractility has been recorded by an intra ventricular latex balloon. Total oxidant and antioxidant status were measured from the serum samples.
Results: Induction of diabetes resulted in an apparent body weight loss, high blood glucose, endothelial dysfunction and increased serum oxidant status. DEX supplementation restored the endothelial dysfunction, antioxidant status and body weight whereas decreasing blood glucose level.
Conclusion: Along with the standard therapy of diabetes, DEX can be used as a safe and economical way of adjuvant therapy to diminish the burden of the disease *(Tab. 3, Fig. 3, Ref. 30)*. Text in PDF *www.elis.sk.*
Key words: endothelium, panthenol, panthotenol, streptozotocin, vitamin B5.

Dysfunction of micro- and macro-vascular system is a critical and initiating cause of morbidity and mortality in patients with diabetes due to its complication on other organs, such as heart, kidney and eye (1, 2). The role of oxidative stress in impaired endothelial function is well established in many of researches (2–4). Therefore, endothelial protection against oxidative stress is one of the key strategies to diminish vascular complication (2, 5). Additionally, myocardial structure and functions also can be affected directly without coronary disease in diabetes and recognized as another clinical entity (6). There is a growing awareness that natural vitamins prevent the endothelial dysfunction associated with an enhanced oxidative stress in diabetes (4, 5, 7, 8).

Streptozocin (Streptozotocin, STZ) is well known chemical agent for the induction of diabetic metabolic state in experimental animals and can also produce a suitable model of vascular complications in diabetes (3, 9).

Although many earlier researches revealed that panthothenic acid (PA) and its precursor dexpanthenol (DEX) had a beneficial effect in several clinical or experimental conditions including Pantothenate kinase-associated neurodegeneration (PKAN) (10), liver failure (11), radiation damage (12), ischemia-reperfusion injury of brain (13) and testicular tissue (14), the experimental data focusing on cardio protective effect are still very limited. It has been reported that PA and derivatives should be considered as cardiac protectors throughout increasing ATP content, reducing lactate and malondialdehyde (MDA) level in isolated ischemia-reperfusion heart model (15, 16). Furthermore, the other studies indicate diverse functions of PA such as regulation of coenzyme A (CoA) (17, 18), glutathione synthesis (12, 17) and cholesterol synthesis of cell membranes (19). On the other hand, one of earlier study about the relationship between diabetes and PA demonstrated that PA urinary loss increased and claimed that its utilisation for forming ATP has been deteriorated in both diabetic patients and rats (20). At web database, Micromedex® 1.0 (http//www.thomsonhc.com) recommends some of its indications as atherosclerosis, hyperlipidemia and rheumatoid arthritis.

The aim of this study was to investigate whether (*i*) clinical features such as body weight, blood pressure, heart rate and glucose level is altered (*ii*) cardiac parameters is affected (*iii*) vascular functions (relaxation and contractility) is improved in coronary arteries and aorta (*iv*) (anti)oxidant status is changed by prolonged high dose of PA supplementation in both healthy subject and diabetes.

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Methods

Drugs and chemicals

Phenylephrine hydrochloride (PE), acetylcholine hydrochloride (Ach), sodium nitroprusside (SNP), Bradykinin acetate (BK) and Kreb's chemical salts were purchased from Sigma Chemicals (Interlab, Izmir, Turkey). Dexpanthenol (Bepanthen®, Bayer Turk

Kimya Ltd., Istanbul, Turkey) and IME-DC® Glucosticks (Santek Medikal, Izmir, Turkey) (range 20–600 mg/dL) were gifted. Total oxidant and antioxidant status (TOS/TAS) kit obtained from Rel Assay Diagnostics (Gaziantep, Turkey) (Sensitivity: <10 pg/ml)

Animals

Male Wistar rats, 200–210 g were obtained from Experimental Animal Center of Adnan Menderes University (ADU) and all experiments were performed according to the principles and guidelines of ADU Animal Ethical Committee's approval (HEK/2009/64). The animals were assigned randomly in the four groups as following:

Control: This group rats served as a healthy animal group.

DEX: Healthy animals with DEX treatment only.

STZ: This groups rats were administered a single intraperitoneal (ip.) injection of STZ.

STZ+ DEX: This group was also both given STZ and DEX ip.

Diabetes was induced by a single ip. injection of STZ (50 mg/kg) dissolved in 1 mL 0.9 % NaCl and administered to the rats within 1 minute. STZ applied rats with over than 200 mg/dL glucose levels in tail blood samples 3 days after the injection were considered diabetic and reassessed weekly with the body weights (BW) for confirmation of clinical disease severity. DEX injection started from the first day of the working groups 300 mg/kg/day ip. and the doses of animals were adjusted every Monday according to their weight changing during 6 weeks course. Systolic blood pressure (SBP) and heart rate (HR) were also recorded by using the tail cuff method (NIBP200A, Commat Ltd., Turkey) at the beginning and end of the study for each animal.

Experimental design

Under the Ketamine and Xylasine (50 mg/kg and 5 mg/kg, respectively) anaesthesia, heart tissues were immediately immersed with heparinised cold Krebs Henseleit solution (KHS) of the following composition (in mM): NaCl 118.1, KCl 4.56, $CaCl_2$ 1.22, $MgSO_4$ 1.22, KH_2P04 1.1, $NaHC0_3$ 25, D-glucose 10.1 to clean an excess blood of coronaries for no more than 1 minute prior to Langendorff apparatus. After suspended, the hearts were perfused retrogradely by aortic cannula at a constant flow rate with oxygenated KHS at 37 °C. Coronary perfusion pressure (CPP) was monitored as an index of coronary micro vascular tone. Myocardial contractile function was assessed by inserting a fluid-filled latex balloon in to the left ventricle. Left ventricular developed pressure (LVDP), and the positive and negative differentiated pressures (+d*P*/d*t* and -d*P*/d*t*) as an index of inotropism and relaxation, respectively were calculated. After stabilisation period for 20–25 minutes, initial KHS was changed to another, which contained 3.2 mM K^+ to obtain an increase in CPP for allowing to vasodilator response to be observed. BK (0.01 μM) and SNP (0.1 μM) were administered to coronary vascular bed as a bolus infusion (21).

Thoracic aortic rings of approximately 3 mm in length were mounted in 20 ml organ baths containing KHS at 37 °C and constantly oxygenated with carbogen. Some of rings denudation was achieved by gently rubbing the intimal layer of the vessel with a small forceps. After 60–90 minutes equilibration period under 2 g resting tension (22), cumulative concentration response curves were obtained by adding to the bath increasing concentration of PE (0.001–30 μM) or KCl (40 mM). Relaxant responses were determined by using cumulative concentrations of Ach (0.001–30 μM) or SNP (0.0001–3 μM).

In the experiments, KHS's in different mM K^+ were obtained by replacing equimolar amount of Na^+ with K^+ to maintain the constant ion strength. Measurement of isometric force was recorded by force transducers (MAY FDT 05, Commat Ltd., Turkey) and a data acquisition system (MP 150, Biopac Systems Inc., USA). At the end of each experiment, wet heart (HW) and dried rings were weighed for further calculations.

Blood samples obtained from the thoracic chest following the excision of heart were centrifuged (1000 X *g* for 10 minutes) and separated serum stored at –80 °C for TOS/TAS measurements. When the all groups` frozen serum samples were gathered, TOS/TAS amounts were measured by a commercially available colorimetric and automated method (23, 24), according to the manufacturer instructions and multiwell plates were read at 450 nm wavelengths by a spectrophotometer (MultiskanGo, Thermo Fisher Scientific Inc, USA).

Data presentation and statistics

Concentration response curves were fitted by nonlinear regression with simplex algorithm and the rings maximum response (E_{max}) and sensitivity (pD_2; -log EC_{50}) were calculated. Clinical values (BW, HW/BW, SBP, HR, blood glucose), cardiac parameters (CPP, LVDP, +d*P*/d*t*, -d*P*/d*t*), coronary and aortic functions data (PE, KCl, Ach, BK, SNP; E_{max} and pD_2 values) and TOS/TAS levels were assessed by using the Mann–Whitney *U*-test. Variance analysis was used to determine a significance among vascular response curves. Results were expressed as the mean ± SEM, $p<0.05$ was considered significant.

Tab. 1. Clinical features and TOS/TAS levels in all experimental groups.

	Body weight(g)	Heart weight/ Body weight (mg/kg)	Systolic arterial blood pressure (mmHg)	Heart rate (beats/min)	Blood glucose (mg/dL)	TOS level (micromolH_2O_2 Equivalent/L)	TAS level (mmolTrolox Equivalent/L)
Control	311±9.5	3.5±0.09	140.6±3.8	457±17.3	132.0±3.5	8.83±1.03	1.27±0.07
DEX	318±10.7	3.3±0.15	141.6±3.9	441±11.9	125.8±4.6	9.33±1.34	1.31±0.06
STZ	175±4.2‡	4.5±0.21‡	114.0±6.1*	477±31.9	> 600	11.70±1.95†	1.53±0.05†
STZ+DEX	254±11.4‡§	3.6±0.10§	137.2±3.6	379±13.2*	518.0±28.7‡	5.91±0.46*	1.47±0.05*

*$p<0.05$, †$p<0.01$, ‡$p<0.001$ *versus* control; p*P*<0.001 *versus* STZ administered group. Values are the mean±SEM of 8 or 10 rats DEX: Dexpanthenol, STZ: Streptozocin, STZ+DEX: Dexpanthenol treated diabetic rats.

Tab. 2. Values of pD_2 and E_{max} to phenylephrine and E_{max} to KCl in all experimental groups endothelium intact/denuded rings.

Contraction (mg/dryweight)	Endothelium intact			Endothelium denuded		
	Phenylephrine		KCl	Phenylephrine		KCl
	E_{max}	pD_2	E_{max}	E_{max}	pD_2	E_{max}
Control	711.5±89.1	6.45±0.08	882.4±118.4	1287.7±101.7	7.17±0.08	1238.7±93.8
DEX	719.3±64.4	6.67±0.13	869.4±110.9	1619.9±222.3	7.66±0.14*	1178.4±168.5
STZ	557.5±78.2	6.27±0.09	673.0±57.3	1149.8±67.2	7.2±0.12	782.1±70.9†
STZ+DEX	881.0±89.8	6.80±0.08*	763.0±67.6	1479.6±106.5	7.9±0.04*	1099.7±87.2

*p<0.05, †p<0.01 *versus* its own control. Values are the mean±SEM of 13 or 16 experiments. DEX: Dexpanthenol, STZ: Streptozocin, STZ+DEX: Dexpanthenol treated diabetic rats.

Results

Clinical features

On the third day of STZ injection, the STZ and STZ+DEX groups showed significantly higher plasma glucose levels (P<0.001). Mega dose injection of DEX in parallel with the administration of STZ did not prevent the development of a diabetic state. Supplementation of DEX did not affect the healthy rats BW, HW/BW, SBP, HR and blood glucose levels compared to the control for 6 weeks period.

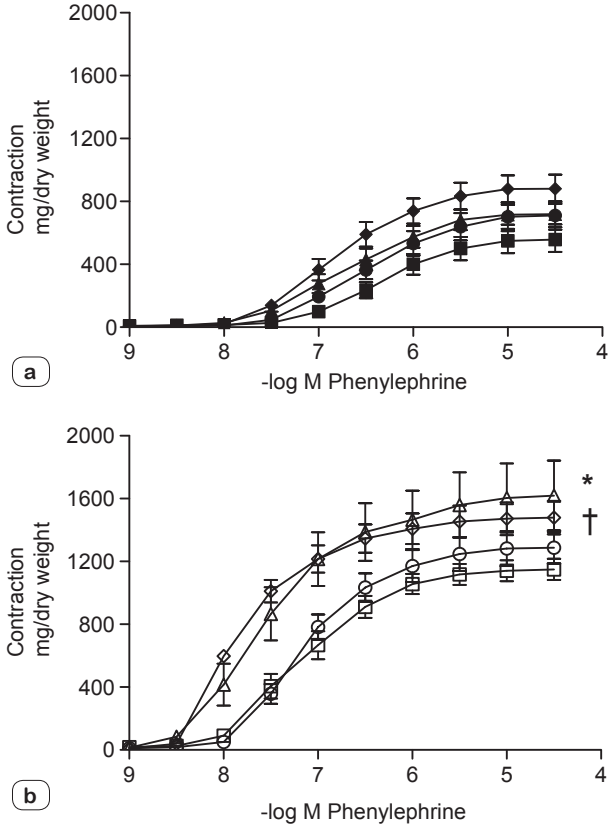

Fig. 1. Concentration-response curves for phenylephrine in control (●,○), dexpanthenol (▲,Δ), streptozocin (■,□), dexpanthenol treated diabetic rats (♦,◊) endothelium intact (a, solid symbols) and endothelium denuded rings (b, open symbols). Values are mean±SEM of 13 or 16 rings. *p<0.05, †p<0.01 *versus* control.

At the end of follow up, STZ rats HW/BW ratio increased (p<0.001) due to dramatic body weight lost (p<0.001) and increased blood glucose level which was higher than aquantitative measurement capability of the strips (>600 mg/dL). Therefore, we were unable to determine the *p* value. SBP decreased significantly (p<0.05) while basal HR tended to increase in STZ group compared to control and DEX treated groups.

DEX treatment reduced the body weight lost, therefore prevented the increasing of HW/BW ratio, restored the SBP while lowering the HR (p<0.05) in STZ rats than control. Blood glucose level decreased to 518±28.71 from higher than 600 mg/dL level. Overall, DEX in vivo treatment significantly improved the clinical aspect of diabetic rats (Tab. 1).

Cardiac parameters

There were no statistically significant differences among the groups in LVDP, +d*P*/d*t* and -d*P*/d*t* value in isolated perfused hearts (Data not shown).

Contractile responses

In coronary vessels, initial CPP was 73.23±8.04 mmHg in the control hearts and 58.85±5.51, 84.32±8.26, 81.13±4.94 mmHg in DEX, STZ, STZ+DEX hearts respectively. The two STZ intervention groups' pressure was slightly higher than in the control prior to changing the KHS, but not significant. When perfusate's K^+ concentration reduced from 5.9 to 3.2 mM, healthy rats and DEX groups CCP value increased additionally 40.16±7.80 and 32.59±3.99 mmHg, respectively. This contraction capability was significantly lower in STZ group, 14.26±4.83 mmHg (p<0.01). DEX treatment ameliorated the contractile function of diabetic rats coronary (19.60±4.94 mmHg, p<0.05), but it remained effected.

In the endothelium intact aorta, only STZ+DEX group's sensitivity increased to PE, the other rings concentration response curve, E_{max} and sensitivity were insignificant (p<0.05) (Tab. 2). Endothelium denuded rings PE contractility was considerably higher and the sensitivity was also increased compared to endothelium intact counterparts (p<0.001, p<0.05) (Fig. 1, Tab. 2). Denuded rings concentration response curves shifted to the left in DEX and STZ+DEX treatment groups (p<0.05, p<0.01, respectively) without changing E_{max} value (Tab. 2, Fig. 1B).

There were no differences to KCl among the rings with endothelium. Denudation of endothelium increased KCl response except STZ group, diabetic rings contractile function found deteriorated (p<0.01) and this impairment restored by DEX (Tab. 2).

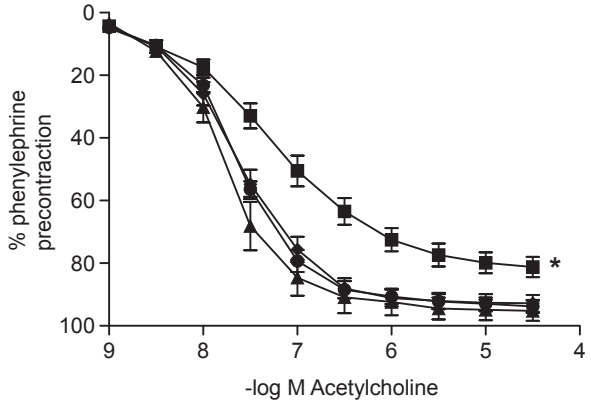

Fig. 2. Concentration-response curves for acetylcholine in control (●), dexpanthenol (▲), streptozocin (■), dexpanthenol treated diabetic rats (♦). Values are mean±SEM of 9 or 12. *p<0.01 *versus* control.

Relaxant responses

Coronary vasodilator responses to BK diminished to 27.80±3.36 ($p<0.01$) with diabetes compared to the control and DEX hearts 44.22±3.39, 41.54±5.19, respectively. DEX treatment in STZ rats completely restored coronary endothelial relaxation to 48.45±3.00. An endothelium independent relaxant agent, namely SNP, produced similar results. 17.11±2.62, 21.81±3.54 relaxation percents obtained from the control and DEX groups. While diabetes impaired the response to 7.92±1.77 ($p<0.01$), DEX treatment completely normalized the smooth muscle relaxation to 17.54±2.00.

After precontracted with PE, Ach and SNP induced relaxations in all aortic rings (Figs 2 and 3, respectively). The pD_2 values and the maximum relaxations expressed as percentage of their corresponding to PE precontraction are given in the Table 3. STZ group Ach concentration response curve shifted to the right ($p<0.01$) (Fig. 2), both relaxation (E_{max}) and sensitivity diminished significantly ($p<0.01$) (Tab. 3) and this amelioration was completely prevented by DEX in STZ+DEX rings (Fig. 2, Tab. 3).

There were no significant differences among the SNP response curves, E_{max} and pD_2 values to in any group, almost 100 % relaxations were obtained ($p<0.05$) (Fig. 3, Tab. 3).

TOS/TAS levels

When compared to the control, DEX treated rats TOS/TAS levels were not different. STZ treated group presented a dramatic increase in TOS/TAS (both $p<0.01$) capacity. DEX treatments lowered the TOS increment more than even the control value ($p<0.05$) while TAS capacity remained high ($p<0.05$) (Tab. 1).

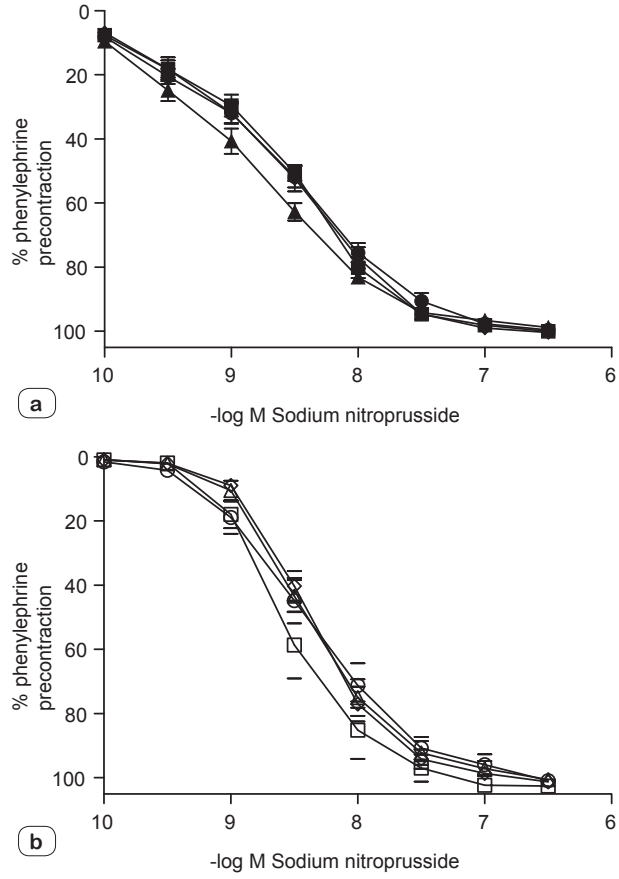

Fig. 3. Concentration-response curves for sodyum nitroprusside in control (●,○), dexpanthenol (▲,Δ), streptozocin (■,□), dexpanthenol treated diabetic rats (♦,◊) endothelium intact (a, solid symbols) and endothelium denuded rings (b, open symbols). Values are mean±SEM of 9 or 12 rings.

Discussion

In the present study, we considered the possibility that PA supplementation might reduce the disease severity and prevent the endothelial cell injury observed in STZ induced diabetic rats by decreasing the oxidative stress. Six principle outcomes were obtained from this study. First, a high intake of long term PA did not harm (anti)oxidant mechanisms, clinical, cardiac and vascular

Tab. 3. Values of pD_2 and E_{max} to acetylcholine and sodium nitroprusid in all experimental groups endothelium intact/denuded rings.

% Phenylephrine precontraction	Endothelium intact				Endothelium denuded	
	Acetylcholine		Sodium nitroprussid		Sodium nitroprusid	
	E_{max}	pD_2	E_{max}	pD_2	E_{max}	pD_2
Control	93.9±2.09	7.64±0.07	99.6±1.52	7.47±0.07	100.9±0.99	7.39±0.13
DEX	95.3±3.24	7.80±0.13	98.8±1.50	7.76±0.08	100.6±1.56	7.39±0.09
STZ	81.3±3.25*	7.21±0.11*	100.1±0.74	7.50±0.07	102.6±0.88	7.55±0.15
STZ+DEX	92.9±2.74	7.60 ±0.08	100.4±0.95	7.50±0.08	101.3±0.89	7.36±0.08

*p <0.01 *versus* control. Values are the mean±SEM of 9 or 12 experiments. DEX: Dexpanthenol, STZ: Streptozocin, STZ+DEX: Dexpanthenol treated diabetic rats.

variables in healthy subject. Second, clinical findings of diabetes in animals such as hyperglycaemia, body weight lost, blood pressure and heart rate lability were modified by PA. Third, whereas an increased oxidative stress due to diabetes highly diminished after treatment, antioxidant capacity remained elevated. Forth, vasoconstrictor function partially restored in coronaries, improved in aorta to KCl, but increased in aorta to PE after PA treatment. Fifth, diabetic smooth muscle relaxation to SNP in coronaries and endothelial responses to Ach in coronary/aorta completely recovered with the treatment. Sixth, myocardial pathologic signs did not obtain after 6 weeks of STZ intervention in isolated Langendorff heart apparatus.

Large body of researches reported the protective effect of different kinds of vitamins on cardiovascular system or/and diabetes. For example, tiamin (B1) therapy is suggested for diabetes and its complication and prevents the development of STZ induced diabetes in rats, high dose of Biotin (B7) decreases fasting glucose level in type II diabetics (18), ascorbic acid only partially enhances the vasodilatation response in diabetes (25). Whereas vitamin E and C treatments prevent cardiovascular complication in diabetic model (5, 7, 8); contrarily, high dose vitamin E and C combined supplementation showed a deleterious effect on endothelium in control rats (7) and high intakes of niacin (B3) might produced insulin resistance (18).

In the previous reports, it has been noticed that the dose of PA that has been used highly differed among studies (13, 14, 26). We have chosen 300 mg/kg/per day, which is also the suggested dose of atherosclerosis treatment (Micromedex®, 1.0). PA's safety was proven on clinical variables by following BW, HW/BW, SBP, HR, blood glucose and TOS/TAS capacity changing on healthy rats for 6 weeks.

When diabetic rats were treated, DEX decreased the excess weight lost. Although PA is reported as a weight losing agent at Micromedex® data base and has been found effective against hypothalamic obesity of rat model (26), another study has reported panthenol-treated animals exhibited less body weight loss in middle cerebral artery occlusion model (13). These reports support our finding that PA has an important agent on modulation of body weight. During the 6 weeks of follow up period, glucose level always remained 10–15 % lower compared to the non-treated rats. The interest should be focused on PA as an important regulator of glucose metabolism. It has been postulated that PA effect are related to lipolysis activation and reduced insulin resistance in hypothalamic obesity model (26). Increasing the glucose utilization on tissue level might be the explanation for both weight gain and glucose lowering effect. Furthermore, blood pressure normalized with treatment was most probably due to prevention of polyuria and dehydration. PA's vital metabolic role has been pointed out in 1967 and vitamin loss, possible the results of impaired renal tubular reabsorption determined in both diabetic patients and rats (20). Additionally, these researchers suggested neuropathies of diabetes may result from abnormalities of its metabolism, impaired conversion of PA or utilisation for forming ATP in the body.

There has been no report from diabetic animal studies investigating the protective effect of PA on vascular functions. In our study, six week of hyperglycaemia diminished the contraction capacity of coronaries. It has been reported that 60 minute acute hyperglycaemia produced a smaller increase in CPP (35 and 12 %) (27), which supports our finding. Both Ach and BK release nitric oxide (NO) and relaxation indexes are a trustful marker for endothelial integrity in vascular studies (21). In this study, coronaries BK relaxation was completely deteriorated as expected. SNP releases NO and stimulates cGMP directly for relaxation of the smooth muscle (21). Although it has been found normal after an acute hyperglycaemia (27), our experiment showed that this mechanism was also affected with the disease progression. It is noteworthy here that PA treatment completely reversed all these impairments of coronaries.

In regards to macro vascular experiments, PE and KCl evaluated aortas smooth muscle contractile capability of receptor- and voltage-dependant manner, respectively (21). Previous researches suggested PE response augmented both in endothelium-intact (8, 25) and -denuded rings (8). However, in this study, there were not any differences to PE similar to another paper (4), and to KCl in the rings with endothelium. When the endothelium mechanically denuded, all rings PE contractility increased due to the loosing of endothelium's depressor effect. Meanwhile, DEX and STZ+DEX treatment groups' smooth muscle sensitivity increased to PE more than the control and STZ groups through the receptor depending mechanisms on calcium influx without changing the maximum response. Increased CoA level by PA (17) might be responsible for the production of prostaglandins and prostaglandin-like compounds (28). In the present study, prostanoid synthesis inhibitors were not used and the involvement of PA on which contractile mediator's formation and bioavailability was altered requires further investigations. Additionally, endothelium-denuded diabetic rats clearly demonstrated low KCl response, contrary to one research mentioning there was not any change in denuded ring (8) and PA restored this dysfunction of the voltage channels. Diminished Ach response was clearly demonstrated in our research and is in agreement with the diabetic animal studies (4, 7, 8, 29). Although one study showed SNP responses was significantly reduced in diabetes (25), the others (4, 7, 8) expressed similar results as this study that it was not changed. The conflict of current data about the vascular reactivity to PE, KCl and SNP might be the results of the rats strain and time course of diabetes model. The present study revealed that there was a selective impairment in endothelium-dependant relaxation of macro vascular system in diabetes. Both reduced contraction and relaxant responses in coronaries demonstrated that coronary stiffness occurred before than aortas at the end of six weeks and suggested that small arteries destruction started in early phase of animal model.

An increased production of oxygen-derived free radicals (ROS) and/or decreased free radical scavenger systems have been described as underlying mechanisms of altered vascular reactivity (1, 3, 30). Endothelium produces NO which is the main regulator of blood vessel tonus. When the endothelium is damaged by chronic diseases including diabetes and hypertension, an increased ROS production and lipid peroxidation reduces NO bioavailability, hence the contractile function augments (2, 4, 8). We demonstrated

that diabetes increased the oxidative stress by 32.5% and possibly as a compensation of the new situation, antioxidant mechanisms also enhanced by 20.47 %. DEX treatment showed by 49.49 % reduction on TOS level while TAS level remained by 15.75 % significantly higher than control. Supplement of vitamin B5 stores led to the improvement in both vascular tissues contractile and relaxant functions by reducing the oxidative stress.

The review by Wojtczak and Slyshenkov corroborated molecular mechanisms of how PA and derivatives exerts their effect in detail (12). The prominent mechanism is based on antioxidant defence system, especially on glutathione synthesis (12, 17), which involves in variety of metabolic functions including detoxifying metabolites, scavenging free radicals, regulation of enzyme activities and DNA repair (11). Due to the lack of catalase in mitochondria, mitochondrial depletion of glutathione led to an increase ROS and reactive nitrogen species, mitochondrial dysfunction and ATP depletion, resulted in apoptosis and necrosis (11, 30). It has been clearly postulated that insulin deficiency led to a decreased glutathione synthesis, therefore antioxidant defence impaired in diabetes (11). As a result of glutathione depletion, endothelial cells became extremely vulnerable to oxidative stress (30). Moreover, PA regulated acetyl CoA synthesis (17, 18) to protect the cells from ROS by stimulating removal of lipid peroxides and potentiating membrane repair mechanisms and cholesterol synthesis (19).The oxidative stress markers, increased aldehyd formation and lipid peroxidation, can be assessed by MDA level in experimental studies (8, 14). Serum MDA level decreased by 500 mg/kg DEX, hence testicular tissue injury alleviated in ischemia-perfusion model (14). Pantethine MDA reducing effect has been found in 57.4 % in myocardium (15). Furthermore, ATP synthesis increased in cardiac (16) and lymphoblastoic cells by PA treatment (17).

In addition to (anti)oxidant mechanisms, acetyl CoA is used for synthesis of Ach (13), which induces its endothelial muscarinic receptors, stimulates NO release and further results in vasorelaxation (8). It is reported that glutathione also regulated NO homeostasis (11). Co-existence of enhanced production of ach and glutathione modified the vascular tonus.

Changes in myocardial structure, calcium signalling and metabolism were described as an early defects in animal models and manifested cardiac dysfunction without coronary or hypertensive disease in diabetes (6). In our study, we could not see any deterioration in cardiac function in Langendorff heart method by following left ventricular pressure, inotropism and relaxation index of cardiac muscle in four groups. These findings suggested that six weeks were not enough for cardiac damage in animal model.

Conclusion

STZ diabetes model produced an endothelial damage and systemic inflammatory response by inducing ROS. DEX supplements protective effect should be the co-existence of all modulator factors such as of body weight, impaired glucose tolerance, lipid metabolism and at some point by regulating the (anti)oxidant mechanisms. The requirement in non-toxic endothelial protectors is of great importance in clinical success of diabetes/cardiovascular disease treatment. To our best knowledge, this is the first study about lone vitamin B5 treatment on diabetes clinical symptoms and cardiovascular tissue damage. It was well tolerated, highly safe and cost effective potent adjuvant therapy for preventing diabetes cardiovascular complications.

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