The effect of Losartan, angiotensin Ⅱ type 1 receptor antagonist, on ß-cells in diabetic animal model

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The effect of Losartan, angiotensin Ⅱ type 1 receptor antagonist, on ß-cells in diabetic animal model

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(Abstract)

The effect of Losartan, angiotensin Ⅱ type 1 receptor antagonist, on ß-cells in diabetic animal model

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The local RAS (rennin-angiotensin system) and inflammatory cytokine IL-1ß of play an important role in pathophisoligic process pancreas. In obesity-induced insulin resistant state, IL-1ß is induced by hyperglycemia in the pancreatic islets. Up-regulation of IL-1ß causes increase in angiotensin Ⅱ type 1 receptor (AT1R) receptor expression. Increased expression of AT1R accelerates ß-cells dysfunction by producing of reactive oxygen species through activation of NADPH oxidase, which results in failure of insulin secretion and impaired plasma glucose

homeostasis. We hypothesized that blocking AT1R in pancreatic islets by Losartan will prevent ß-cells from their dysfunction induced by ROS and inflammatory cytokines through inhibition of down stream signals of AT1R. In this study, we determined the effect of Losartan on ß-cells in diabetic animal model.

Fasting plasma glucose level was significantly elevated by Losartan at 30mg/kg/day in rats fed high fat diet. The expressions of IL-1ß, AT1R and p22phox were increased in pancreatic islet of rats fed high fat diet. However, Losartan treatment significantly improved glucose tolerance and decreased the expression of IL-1ß, AT1R and p22phox.

These results suggest that Losartan, a angiotensin Ⅱ type 1 receptor antagonist, improves beta cell function by decreasing the expression of IL-1ß, AT1R and p22phox in pancreatic islets.

Key words: ß-cells, AT1R (Angiotensin Ⅱ type 1 receptor), Interlukin-1ß (IL-1ß), p22phox, Losartan (Angiotensin Ⅱ type 1 receptor antagonist)

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Ⅰ. INTRODUCTION

Obesity-induced type 2 diabetes mellitus (T2DM) is a worldwide epidemic and an severe public health problem. Pancreatic beta-cell failure is considered as a key process in the development of T2DM.[1, 2] The mechanism of beta-cell dysfunction in T2DM is complex. ß-cells dysfunction in individuals with insulin resistance and glucose intolerance is known to be aggravated by glucose, free fatty acids and factors derived from adipose tissue. [3] Once stimulated by these factors, ß-cells adapt to the condition by increasing the number of functional ß-cells. However, as the

insufficient compensation of insulin function persists, ß-cells fail to meet the need for hormonal glucose homeostasis, end in loss of ß-cell mall with insulin deficiency and hyperglycemia. Long-term elevation of plasma glucose concentration induces ß-cell apoptosis. [4, 5] As the impairment of ß-cells persists, it accelerates the progress of T2DM. Oxidative stress leads to tissue damage by oxidizing and damaging DNA, proteins and lipids. [6] NADPH plays an important role in ß-cells dysfunction and apoptosis by producing superoxide. NADPH oxidase is a multiensymatic electron transfer complex which catalyses the production of superoxide by transferring electrons from NADPH to molecular oxygen.[7] ß-cells express significant amounts of NADPH oxidase, while they are. [8, 9] ß-cells are known to be sensitive to reactive oxidative stress (ROS) because the activity of antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase are low. The ROS of beta cell activated by NADPH oxidase subunits decreases insulin gene expression and causes beta cell apoptosis.

AT1R is expressed in ß-cells and up-regulated in pancreatic islets in diabetic animal model. Recently, it is suggested that angiotensin II activate NADPH oxidase which in turn promotes ß-cell dysfunction and apoptosis by induction of oxidative stress. [10, 11, 12, 13] However, administration of an

AT1R antagonist inhibited oxidative stress by down-regulation of NADPH oxidase; thus decreases ß -cell apoptosis and improves ß -cell function. [10, 11, 12, 13]

Pro-inflammatory cytokine interlukin-1ß (IL-1ß) is increased in pancreatic islets of diabetic patients. [14] ß-cells under hyperglycemic condition hyperglycemia induce endogenous production of IL-1ß through Fas activation. [15] There are evidences that IL-1ß enhance expression of AT1R in heart and brain. [16, 17] However, it is unknown whether IL-1ß increase AT1R expression in pancreatic ß-cells. In this study, it is hypothesized that IL-1ß was increased in pancreatic islets of diabetic animal accompanying metabolic stress and glucose intolerance. NADPH oxidase is the enzyme that plays a pivotal role in ß-cell dysfunction and apoptosis. Because NADPH oxidase is an enzyme that plays a pivotal role in ß-cell dysfunction and apoptosis, I determined the effects of Losartan, an AT1R antagonist, on IL-1ß and NADPH oxidase in ß-cells of diabetic animal models.

Ⅱ. METERIALS AND METHODS

1. Chemicals

Losartan potassium (Cozaar®) was purchased from Merck (E.I.du Pont de Nemours & Company, Wilmington, Delaware, U.S.A.). Normal chow diet was purchase from LabDiet® (U.S.A.). All other chemicals and regents that were not noted in methods were purchased from Sigma Aldrich (St. Louis, MO, U.S.A.).

2. Experimental conditions

Otsuka Long-Evans Tokushima Fatty (OLETF) rats were provided from Otsuka Pharmaceutical (Tokushima Research Institute, Japan). All the animal experiments were performed in accordance with guidelines for Animal research from AAALAC International and approved by Department of Yonsei Aminal Research Committee. The animals were housed in cages under 12/12-h light/dark cycles. OLETF rats aged 32 weeks were divided into three groups: control-diet group (Con, n= 10), high-fat diet group (HF, n= 10), and high-fat diet with Losartan-treated

group (HF+Los, Losartan dissolved in drinking water, n=10). Losartan was given orally in a daily dose of 30 mg/kg/ml by gavage. Body weight was determined at 9 am before and the administration of Losartan. Three weeks ofter Losartan administration, rats were anesthetized with Zoletil 50 (Virbac Laboratories, France) and sacrificed for tissue sampling.

3. Biochemical examination

Blood was collected by heart puncture. Plasma concentration of triglyceride (Thermo Fisher Scientific, Waltham, MA, U.S.A.) and total cholesterol (Thermo Fisher Scientific, Waltham, MA, U.S.A.) were measured by according to the manufacturer's instructions.

4. Oral glucose tolerance test

After overnight fasting, an oral glucose tolerance test using 20%(w/v) glucose solution (2 g/kg) was performed. Blood samples were obtained by tail snipping. Blood glucose levels were measured using Accu-Check (Roche). Glucose concentration was measured at 0, 15, 30, 60, and 120 min after glucose administration.

5. Immunostaining analysis

For immunostaining analysis of AT1R, IL-1ß, and p22phox, pancreas was removed and fixed in 10% formaldehyde, then embedded in paraffin and section according to the standard protocol. After inactivation of endogenous peroxidase with 3% H_2O_2 in methanol for 15 min at room temperature, samples were incubated with anti - mouse AT1R (Santa Cruz Biotechnology, CA, U.S.A.), anti - rabbit IL-1ß (Santa Cruz Biotechnology, Santa Cruz, CA, U.S.A.), or anti-rabbit p22phox (Santa Cruz Biotechnology, CA, U.S.A.) overnight at 4 C, washed in PBS, and probed with secondary antibodies conjugated with peroxidase for 1 hour at room temperature. Sections were counterstained with hematoxylin before being examined under a light microscope. The stained area on AT1R, IL-1ß, p22phox of total islets was measured using image analysis software.

6. Statistical analysis

Data are presented as means ± standard deviation. Statistical significance between groups was calculated by Student *t*-test. A value of $P < 0.05$ was considered to statistically significant.

Ⅲ. RESULTS

1. Basic characteristics

There were differences in weight loss between high fat fed group and high fat fed group treated Losartan. The initial body weight of high fat fed group and high fat fed group treated Losartan were 666 ± 28 g and 665 ± 27 g, respectively. After treatment of Losartan for 3 weeks, body weight in high fat fed group treated Losartan was lower than that in high fat fed group (693 ± 39 g vs. 615 ± 49 g) (Table. 1).

Table. 1. Comparison of basic characteristics between control, high-fat, and high-fat diet supplemented with Losartan.

	Control	High-fat	High-fat+Los
Initial body weight,g	601 ± 65	666 ± 28	665 ± 27
Final body weight,g	621 ± 80	692 ± 39	615 ± 49
Total cholesterol (mg/dL)	99 ± 10	127 ± 25	118 ± 36
Triglycerides (mg/dL)	177 ± 76	150 ± 67	89 ± 26

Values are means ± SD. Control; normal chow diet, High-fat; high-fat diet, High-fat+Los; high-fat diet supplemented with Losartan.

2. Oral glucose tolerance test

Oral glucose tolerance test was performed at the end of the experiment. Fasting plasma glucose concentration of Losartan-treated group was lower than high fat fed group and similar with that of normal diet. Fasting plasma glucose concentration of Losartan-treated group was entirely showed the tendency to decrease at all checked points compared with high fat fed group. Losartan-administrated group was normalized glucose intolerance compared to high fat fed group (Fig. 1).

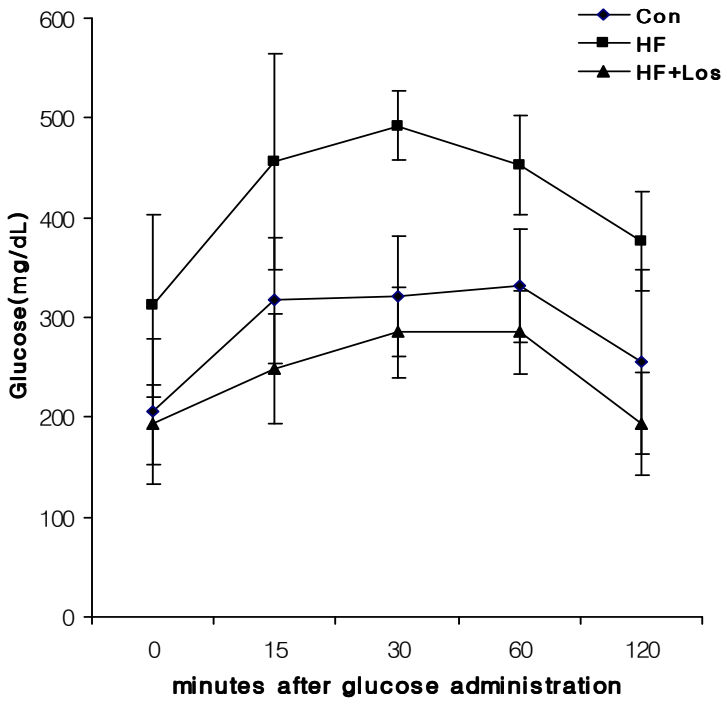

Fig. 1 . Effect of Losartan (30 mg/kg) on oral glucose tolerance test in normal diet, high-fat group and high fat+losartan group. Plasma glucose concentration in OLETF rats undergoing oral glucose tolerance test after treatment with Losartan for 3 weeks. DATA are means ± SD. Con (Normal chow diet), HF (High fat diet, 40% fat), HF+Los (High fat diet + Losartan treatment, 30mg/kg/day Losartan).

3. Immunohistochemical analysis of AT1R

Immunohistochemical analysis showed that the expression of revealed the increase of AT1R was increased in HF group by 5.16-fold compared to Con group, whereas it was reduced by 63.8 % in HF + Los group compared to that in high-fat group (Fig. 2).

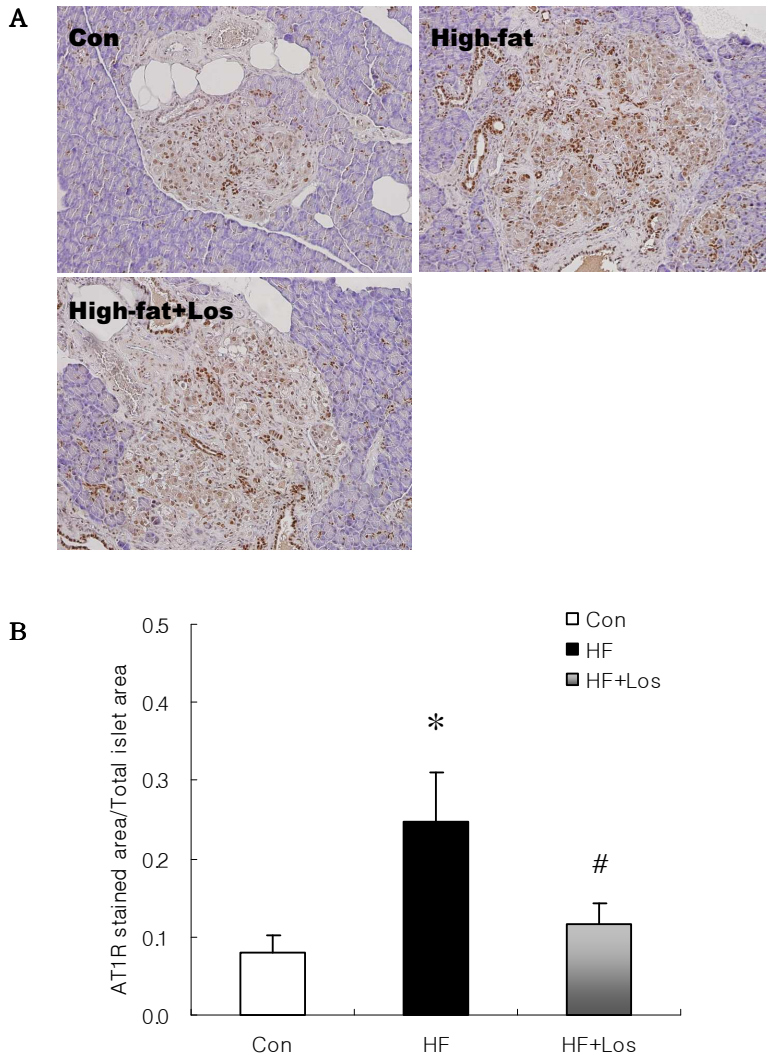

Fig.3. (A) Immunohistochemical staining of pancreatic islets for AT1R. Magnification 200X. (B) The ratio of stained area of AT1R in pancreatic islets. DATA are mean ± SD. Con (Normal chow diet), HF (High fat diet, 40% fat), HF+Los (High fat diet + Losartan treatment, 30mg/kg/day Losartan). *, $P<0.05$ from Con and HF, $^{\#}$, $P<0.05$ from HF and HF+Los

3. Immunohistochemical analysis of IL-1ß

Immunohistochemical analysis showed that the expression of revealed the increase of IL-1ß was increased in HF group by 4.27-fold compared to Con group, whereas it was reduced by 73.35 % in HF + Los group compared to that in high-fat group (Fig. 2).

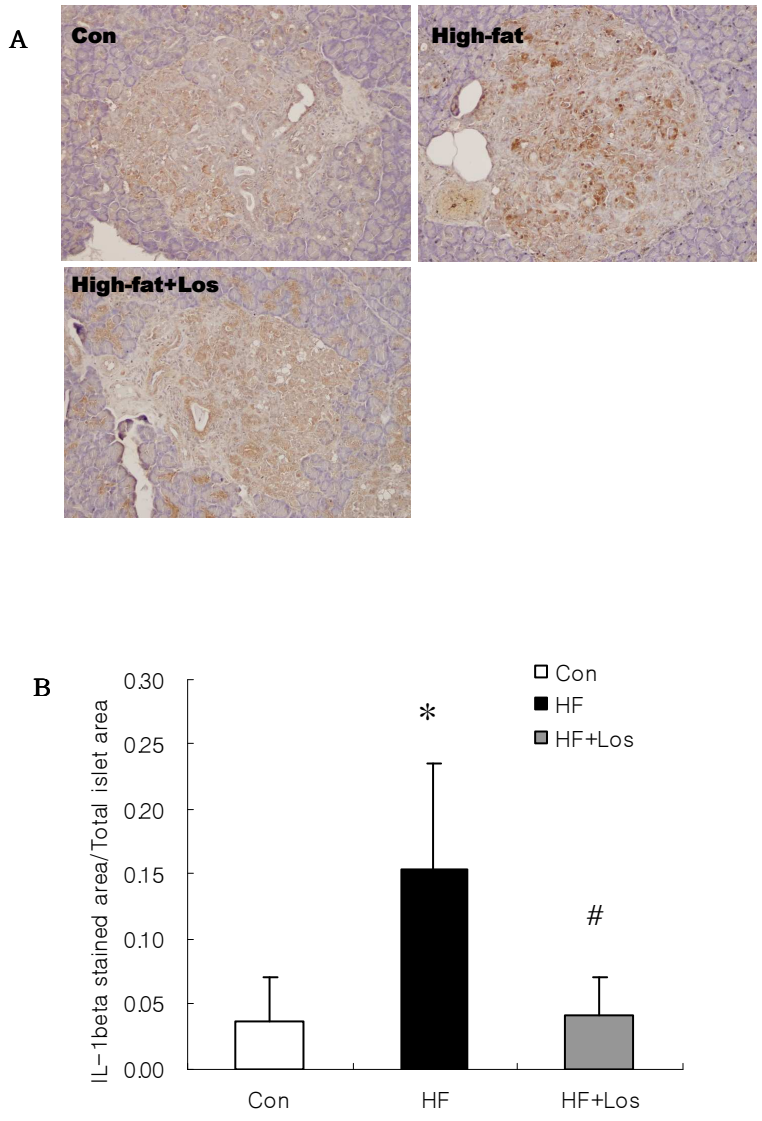

Fig.3. (A) Immunohistochemical staining of pancreatic islets for IL-1ß. Magnification 200X. (B) The ratio of stained area of IL-1ß in pancreatic islets. DATA are mean ± SD. Con (Normal chow diet), HF (High fat diet, 40% fat), HF+Los (High fat diet + Losartan treatment, 30mg/kg/day Losartan). *, *P*<0.05 from Con and HF, $^{\#,}$ *P*<0.05 from HF and HF+Los

3. Immunohistochemical analysis of p22phox

p22phox, a NADPH oxidase subunit, was increased in high-fat group by 2.34-fold compared to normal diet fed group, in contrast, it was significantly decreased by 35.48% in high-fat + Los group compared to high-fat group (Fig. 4).

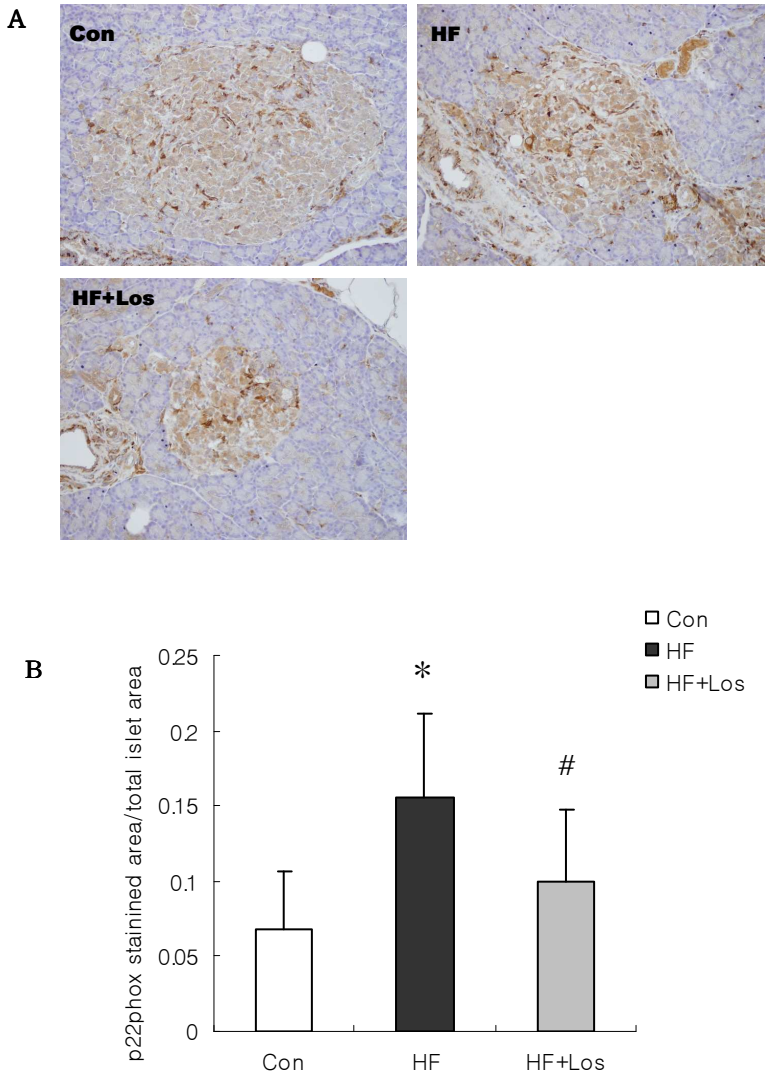

Fig.3. (A) Immunohistochemical staining of pancreatic islets for p22phox. Magnification 200X. (B) The ratio of stained area of p22phox in pancreatic islets. DATA are mean ± SD. Con (Normal chow diet), HF (High fat diet, 40% fat), HF+Los (High fat diet + Losartan treatment, 30mg/kg/day Losartan). *, *P*<0.05 from Con and HF, #, *P*<0.05 from HF and HF+Los

Ⅳ. DISSCUSION

The major pathogenesis of T2DM is ß-cell dysfunction. However, the molecular mechanisms involved in ß-cell dysfunction remain to be elucidated. Recently, RAS in pancreas may play a novel role in islet function and the development of diabetes. RAS have multiple functions in tissues and organ including proliferation, apoptosis, and ROS production[18.] There are also evidences that AT1R expression was up-regulated in pancreatic islets of diabetic animal model and induced ß -cell failure via activating NADPH oxidase which plays an important role for production of ROS7. [11, 12, 13] However, Blocking AT1R activity through administration of Losartan, an Angiotensin II type 1 receptor antagonist, causes anti-apoptotic effects by inhibiting NADPH oxidase activity, which in turn increases synthesis of insulin biosynthesis and glucose-stimulated insulin secretion. [10, 12, 13] However, the precise mechanism on the pancreatic ß -cell function mediated by AT1R remains unknown. In this study, I focused on AT1R activation associated with ß-cell dysfunction. I confirmed that Losartan improved glucose tolerance in high-fat diet-induced diabetic OLETF rats, indicating the preservation of ß-cell function. This result was consistent with previous reports showing the beneficial effects of Losartan

on glucose intolerance. Several studies have reported the involvement of AT1R expression and angioteinsin II in patients with diseases such as IgA nephropathy, in cell culture or in specific tissue of animal model. [19, 20, 21] Expression of AT1R was increased in pancreatic islets of diabetic mouse models.[13] However, the cause increasing AT1R in pancreatic islets of diabetic animal model was not elucidated. The expression of AT1R expression in high-fat diet induced diabetic OLETF rats and Losartan significantly reduced the expression of AT1R. These results suggest that the possibility of increasing AT1R to activate NADPH oxidase, which induces ROS, more significantly than it does not. The expression of IL-1ß, a pro-inflammatory cytokine, was reported to be increased in insulin resistant mice fed high fat diet compared with them fed low fat diet [22] and *ob/ob* mice. It is also reported that IL-1ß is found in the ß -cell of T2DM patients. [23] However, It has not been determined whether IL-1ß increase AT1R expression in ß -cell of pancreatic islets. In this study, I showed that the expression of IL-1ß was increased in OLETF rats fed a high fat diet, while Losartan reduced this increase in IL-1ß. The expression of p22phox, the membrane component of NADPH oxidase and a down-stream effector of AT1R, showed correlated changes with the expression of IL-1ß and AT1R by Losartan. The induction of oxidative stress by activating NADPH

oxidase could result in increased rate of apoptosis of ß -cell, [7] which in turn could trigger ß -cell dysfunction. These results suggest that Losartan ameliorates the ß-cell function by reducing the synthesis of IL-1ß, resulting in reduction of AT1R and p22phox expression in diabetic OLETF rats induced by high-fat diet.

Ⅴ. CONCLUSION

In this study, Losartan, an AT1R antagonist, showed down-regulation of AT1R expression which was caused by increase in IL-1ß. These results suggest that Losartan exert beneficial effects on ß -cell dysfunction in diabetic condition regulation of IL-1ß eta. The precise mechanism of AT1R-mediated beta-cell dysfunction associated with IL-1ß in T2DM is requires to be further studied.

REFERENCE

1, Porte D. Beta-cells in type II diabetes mellitus. Diabetes 1991;40:166–80.

2. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988;37:1595–1607.

3. Kathrin M. Beta cells in type 2 diabetes – a crucial contribution to pathogenisis. Diabetes, Obesity and Metabolism 2008;10:408-20.

4. Meadler K, Spinas G, Lehmann R Sergeev P, Weber M, Fontana A, et al. Glucose induces beta-cell apoptosis via upregulation of the Fas-receptor in human islets. Diabetes 2001;50:1683-90.

5. Donath M, Gross D, Gerasi E, Kaiser N. Hyperglycemia-induced beta-cell apoptosis in pancreatic islets of Psammomys obesus during development of diabetes. Diabetes 1999;48: 738-44

6. Joseph L, Ira D, Betty A, Gerold M. Are Oxidative Stress-Activated Signaling Pathways Mediators of Insulin Resistance and ß - Cell Dysfunction. Diabetes 2003;52:1-8.

7. Bengtsson SH, Gulluyan LM, Dusting GJ, Drummond GR. Novel isoforms of NADPH oxidase in vascular physiology and pathophysiology. Clin Exp Pharmacol Physiol 2003;30: 849–85.

8. Morgan D, Oliveira-emilio HR, Keane D, Hirata AE, Rocha M, Bordin S, Curi R et al. Glucose, palmitate and pro-inflammatory cytokines modulate production and activity of a phagocyte-like NADPH oxidase in rat pancreatic islets and a clonal ß cell line. Diabetologia 2007;50:359-69.
9. Oliveira HR, Verlengia R, Carvalho CR, Britto LR, Curi R , Carpinelli AR. Pancreatic ß-cells express phagocyte-like NADPH oxidase. Diabetes 2003;52:1457-63.
10. M. Nakayama, T. Inoguchi, T. Sonta, Y. Maeda, S. Sasaki, F.Sawada, et al. Increased expression of NAD(P)H oxidase in islets of animal models of Type 2 diabetes and its improvement by an AT1 receptor antagonist. Biochem. Biophys. Res. Commun 2005;332:927–33.
11. Jiaqing S , Noseki I, Fuki I, Takeshi O, Toyoyoshi U, Tomoaki S, et al. Beneficial effects of candesartan, an angiotensin II type 1 receptor blocker, on β-cell function and morphology in db/db mice. Biochem. Biophys. Res. Commun 2006;344:1224–33.
12. Kwan YC, Po SL. Angiotensin Ⅱ Type 1 Receptor Antagonism Mediates Uncoupling Protein 2-Driven Oxidative Stress and Amelorates Pancreatic Islet ß-cell Function in young type 2 diabetic Mice. Antioxid. Redox Signal 2007;9:869-78.
13. Chu KY, Lau T, Carlsson PO, Leung PS. Angiotensin II Type 1

Receptor Blockade improves beta-Cell function and glucose tolerance in a Mouse Model of Type 2 Diabetes. Diabetes 2006;55:367-74.

14. Kathrin M, Pavel S, Frédéric R, José O, Helen I. Joller-Jemelka HI, et al. Glucose-induced beta-cell production of IL-1ß contributes to glucotoxicity in human pancreatic islets. J. Clin. Invest 2002;110:851–60.

15. Maedler K, Schumann DM, Sauter N, Ellignsgaard H, Bosco D, Baertschiger R, et al. Low concentration of interleukin-1{beta} induces FLICE-inhibitory protein-mediated {beta}-cell proliferation in human pancreatic islets. Diabetes 2006;55:2713–22.

16. Hidemi Y, Tadaatsu I, Kunikazu T, Hirotaka S, Norifumi M, Yoshihiro S, et al. Interleukin-1β enhances the angiotensin-induced expression of plasminogen activator inhibitor-1 through angiotensin receptor upregulation in human astrocytes. Brain research 2006;1073-4:38-47.

17. Gurantz D, Cowling RT, Varki N, Frikovsky E, Moore CD, Greenberg BH. IL-1ß and TNF-α upregulate angiotensin II type 1 (AT1) receptors on cardiac fibroblasts and are associated with increased AT1 density in the post-MI heart. J Mol Cell Cardiol 2005;38:505–15.

18. Paul M, Poyan MA, and Kreutz R. Physiology of local rennin angiotensin systems. Physiol Rev 2006;86:747–803.

19. Chan LY, Leung JC, Tang SC, Choy CB, Lai KN. Tubular Expression

of Angiotensin Ⅱ Receptors and Their Regulation in IgA Nephropathy. J Am Soc Nephrol 2005;16:2306-17.

20. Lai KN, Chen LY, Tang SC, Tsang AW, Li FF, Lam MF, et al. Mesangial expression of angiotensin Ⅱ receptor in IgA nephropathy and its regulation by polymeric IgA1. Kidney Int 2004;66:1403-16.

21. Rui-Wei G, Li-Xia Y, Mao-Quan L, Bei L, Xian-Mei W. Angiotensin II induces NF-κB activation in HUVEC via the p38MAPK pathway. Peptides 2006;27:3269-75.

22. Lagathu C, Yvan-Charvet L, Bastard JP, Maachi M, Quignard-Boulange A, Capeau J, Caron M. Long-term treatment with interleukin-1ß induces insulin resistance in murine and human adipocytes. Diabetologia 2006;49:2162–73

23. Maedler K, Sergeev P, Ris F, Oberholzer J, Joller-Jemelka HI, Spinas GA, et al. Glucose-induced beta-cell production of interleukin-1beta contributes to glucotoxicity in human pancreatic islets. J Clin Invest 2002;110:851– 60.

ABSTRACT(IN KOREAN)

당뇨모델에서 Angiotensin Ⅱ type 1 receptor antagonist (Losartan)이 베타세포에 미치는 영향

<지도교수 차봉수 >

연세대학교 대학원 의과학과

박은미

레닌 엔지오텐신 시스템(rennin - angiotensin system)과 염증성 사이토카인 Interlukin-1ß (IL-1ß)는 췌장의 병리생태에 있어 중요한 역할을 수행한다.

IL-1ß 는 비만에 의하여 유도된 인슐린 저항성을 가진 당뇨병상태의 췌장에서 발현이 증가되어, 레닌 엔지오텐신 시스템의 구성요소인 Angiotensin Ⅱ type 1 receptor (AT1R)의 발현은 증가시키고, 산화스트레스 (oxidative stress)를 유발시키는데 중추적 역할을 하는 것으로 알려져 있는 NADPH 산화효소 (NADPH oxidase)를 활성화 시켜서 췌장의 베타세포의 apoptosis 와 기능적 결함을 촉진시키는 것으로 알려져 있다. 그러나, 아직까지

AT1R 길항제인 Losartan 에 의한 당뇨개선효과에 대한 연구는 진행되지 않은 상태이다. 따라서 본 연구에서는 당뇨유발동물 모델에서 Losartan 을 투여한 후 AT1R, NADPH oxidase, IL-1ß 의 변화를 관찰함으로써 Losartan 의 역할을 검증하고자 하였다. 당뇨동물모델에 정상식이 혹은 고지방식이를 섭취시키고, 췌장에서 IL-1ß, AT1R, p22phox 의 발현 변화를 분석하였고, AT1R 길항제인 Losartan 의 처리를 통해 AT1R 이 선택적으로 억제시킨 후 p22phox 의 활성화, AT1R 및 IL-1ß 의 발현 변화를 분석하였다.

Oral Glucose Tolerance Test (OGTT) 를 통하여 고지방식이에 의한 당뇨유발을 확인하였으며, Losartan 처리 그룹에서 인슐린저항성의 현저한 개선효과를 확인하였다. 또한, 고지방 식이군의 췌장에서 IL-1ß, AT1R, p22phox 의 발현이 증가 되었으나, Losartan 투여군에서 발현이 감소되어 있음을 확인하였다.

이상의 연구결과 Losartan 이 AT1R 의 억제를 통하여 당뇨에서 유발된 베타세포의 기능악화를 완화시킬 수 있을 것으로 사료된다.

핵심 되는 말: 베타세포, AT1R(Angiotensin Ⅱ type 1 receptor), 인터루킨-1 베타(IL-1ß), p22phox, 로잘탄(Angiotensin Ⅱ type 1 receptor)