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Changes of insulin-like growth factor-Ⅰ, IGF-binding proteins, and IGF-Ⅰ carrier protein in streptozotocin-induced diabetic rat

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Abstract : This study was conducted to investigate the effects of streptozotocin-induced (STZ) diabetes on insulin-like growth factor-Ⅰ (IGF-Ⅰ), insulin-like growth factor binding proteins (IGFBPs), and IGF-Ⅰ carrier proteins in serum, liver, and kidney. The levels of total and free IGF-Ⅰ were measured by radioimmunoassay (RIA). The patterns of IGFBPs were determined by western ligand blotting (WLB) analysis. The profiles of IGF-I carrier proteins in serum were determined by column chromatography. The levels of total and free IGF-Ⅰ in serum were lower in STZ-induced diabetic rat than normal rat ($p<0.01$). Similarly, the levels of total IGF-Ⅰ in liver was lowered in STZ-induced diabetic rats. On the other hand, the levels of total IGF-Ⅰ in kidney were increased in STZ-induced diabetic rats compared with normal rats ($p<0.01$). In serum and liver from STZ-induced diabetic rats, the amount of IGFBP-3 was decreased and the amount of IGFBP-2 was increased compared with normal rats. There was a not difference in amount of IGFBP-4 in serum between STZ-induced diabetic rats and normal rats. The serums of normal rats have higher 150kDa carrier proteins than in STZ-induced diabetic rats, whereas, most of 50kDa carrier proteins were found in STZ-induced diabetic rats. These results demonstrate that in STZ-induced diabetic rats, IGF-Ⅰ/IGFBPs system that included functional bioactivity was changed in serum as well as tissues, and these changes may play an important role in pathogenesis of diabetes.

Key words : IGF-Ⅰ, IGFBPs, IGF-Ⅰ carrier proteins, diabetes.

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Introduction

Insulin-like growth factors- I and II (IGFs) are polypeptides structurally similar to insulin and involved in the regulation of growth, metabolism and differentiation[1,2]. Based on its structural and functional homology to insulin, it has been postulated that IGFs are involved in pathogenesis of diabetes caused by the T cell-mediated destruction of the insulin-producing beta cells in the pancreatic islets[3].

IGFs are well known to have insulin like action and growth promoting mitogenic effects, IGFs circulate bound to specific binding proteins (IGFBPs) in blood. Six types of IGFBPs have been found which differ in molecular weight, amino acid composition, and distribution in biological fluids. Because IGFBPs have very high affinity with IGFs that is two-50-fold greater than IGF- I receptor, they control the distribution of the IGFs in serum and various fluids. Also they regulate half life, availability and activity of the IGFs[4,5].

IGFs and IGFBPs have an important role in controlling glucose homeostasis[6] and there is evidence to support their involvement in complications related to diabetes[7]. In addition, experimental and human studies suggested that there are some differences of IGF/IGFBPs system between diabetic and normal state. Also these days, rhIGF- I has been proposed as a potential therapeutic agent in the treatment of diabetes mellitus[3].

Serum IGFs and IGFBPs reflect their tissue concentrations to a various degree. Consequently, mechanisms concerning the pathogenic role of the IGF/IGFBP system in the development of diabetic complications at the tissue level remain speculative[8,9]. IGFs are synthesized by many tissues and are proposed to have autocrine or paracrine effects on proximate target cells as well as endocrine actions mediated via the circulation[10]. The putative effects of diabetes and metabolic control on circulating levels of IGFs and IGFBPs remain controversial[11]. Therefore, in this study, we compared the differences in IGFs/IGFBPs system that included the levels of IGF- I , patterns of IGFBPs and profiles of IGF carrier proteins in serum and tissues between normal and STZ-induced diabetic rats, and investigate the relationships of IGFs/IGFBPs system between serum and tissues from normal and STZ-induced diabetic rats.

Materials and Methods

Experimental animals : Thirty male Sprague Dawley rats weighing 205.3±12.5g were used. The animals were fed normal chow (Jeiljedang, Suwon, Korea) for three weeks, then randomly divided into two groups; control group for control and diabetic group. Diabetes was induced by a single intraperitoneal injection of streptozotocin (45mg/kg body weight, St. Louis, USA) and was confirmed by determination of urinary glucose secretion. During the experimental periods, the rats were housed in the laboratory maintained constant temperature (22±2℃) and controlled 12hrs light/dark cycle. The animals were given free access to food and water during the entire experimental period. Two weeks after diabetes onset, animals were anesthetized following 15hrs fast. Blood samples were taken from the trunk after decapitation, centrifuged at 4℃, 3000rpm for 30min and serum was separated and stored at -70℃ until assayed. Liver and kidney were removed and rinsed with saline solution, wiped with paper towel, and then homogenized with trifluroacetic acid solution (TFA) for total IGF- I , centrifuged at 4℃, 3000rpm for 30min and supernatant was separated and stored at -70℃ until assayed.

IGF- I radioimmuno assay (RIA) : Recombinant human IGF-I was iodinated to a specific radioactivity of 150-300Ci/g, [^{125}I] by the modification of the chloramin-T method. Serum and tissue IGFBPs were separated by the method of Lee and Henricks[12]. Immunoreactive IGF-I was performed by the method of Lee *et al* [13]. 50 μl of polyclonal IGF- I antibody diluted to the 1 : 1000 were added to 100 μl of sample/standard and then incubated for 1 hour at room temperature. Add to ^{125}I-IGF- I 20,000cpm to the samples/standard and then incubated for 18 hours at 4℃. All samples were centrifuged at 3,000 x g for 30 minutes. The supernatant was discarded, radioactivity of the precipitate containing bounding [^{125}I]-IGF-I was counted in the gamma scintillation counter. All assays were performed in duplicate. Inter- and intra assay coefficients of variation for IGF-I

were 8% and 10%, respectively.

Determination of IGFBPs patterns by Western Ligand Blotting (WLB) : Samples was electrophoresed on 12% SDS-PAGE under a non-reducing conditions using the Mini-Protein, and proteins were electroplated onto nitrocellulose membrane. The membrane was blocked with 1% BSA and incubated for 18 hours at 4℃ with 200,000cpm of [^{125}I]-IGF-I in buffer containing 1% BSA and 0.1% Tween 20. After extensive washing in cold buffer, the membrane was dried at room temperature. Finally, it was exposured to X-ray films at -70℃ for 7 days by the method of Hossenlopp *et al* [14].

Neutral column chromatography : To determine the profile of IGF-I carrier proteins (150kDa, 50kDa), 150 μl of pooled serum were incubated with 100,000cpm of [^{125}I]-IGF-I for 18 hours at 4℃. The reaction mixture (50,000cpm) was applied to a Sepacryl S-300 (Pharmacia Biotech : 1× 100cm) column equilibrated in tris buffer (pH 7.4) and calibrated with blue dextran (200kDa) and cytochrome C (50 kDa). The samples were eluted with the same buffer at a flow rate of 6ml/hour. Fractions of 1 ml were collected and assessed for radioactivity.

Statistical analysis : Statistical significance was determined by student's *t*-test. $p<0.05$ was considered significant.

Results

The levels of IGF-I in serum and tissues : The levels of total and free IGF-I in serum and tissues of STZ-induced

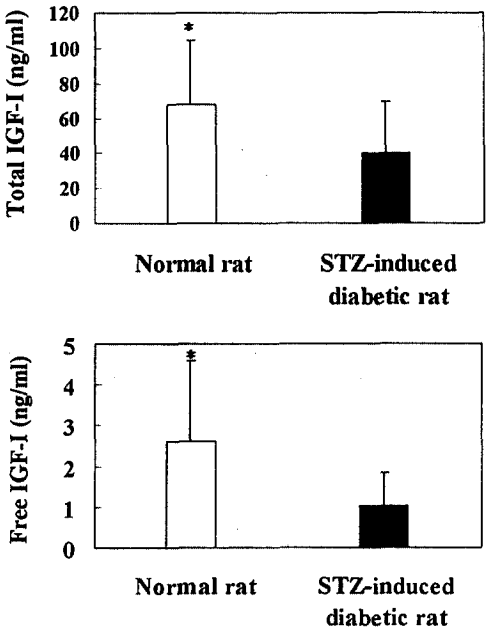

Fig 1. Total and free IGF-I level in serum from normal (□, n = 15) and streptozotocin-induced diabetic rats (■, n = 15). Streptozotocin (45mg/kg) was injected intraperitonealy, and the rats were sacrificed after 2 weeks following diabetes onset. Samples of serum were subjected to acid-ethanol extraction for total IGF-I and the IGF-I levels were measured by radioimmunoassay. Each bar represents the mean±SD of least 15 rats. * indicates significantly difference from corresponding values from normal rats by student *t*-test at $p<0.05$. Upper panel; total, lower panel; free. IGF; insulin like growth factor, STZ; streptozotocin.

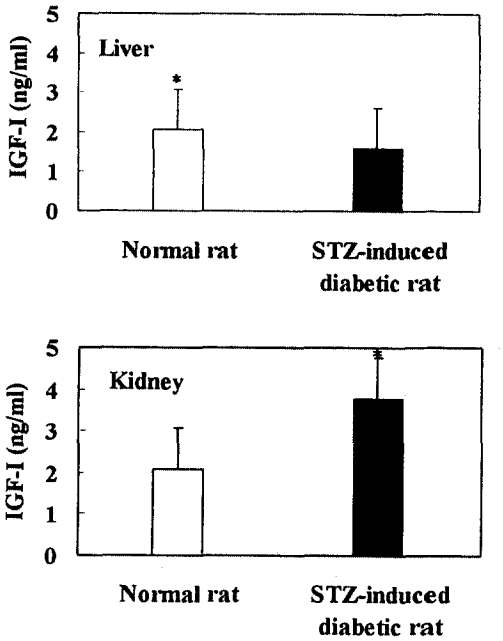

Fig 2. Total IGF-I level in liver and kidney from normal (□, n = 15) and streptozotocin-induced diabetic rats (■, n = 15). Streptozotocin (45mg/kg) was injected intraperitonealy, and the rats were sacrificed after 2 weeks following diabetes onset. Samples of tissues were subjected to acid-ethanol extraction for total IGF-I and the IGF-I levels were measured by radioimmunoassay. Each bar represents the mean±SD of least 15 rats. * indicates significantly difference from corresponding values from normal rats by student *t*-test at $p<0.05$. Upper panel; liver, lower panel; kidney. IGF; insulin like growth factor, STZ; streptozotocin.

diabetic rats and normal rats were measured by RIA. As shown in Fig 1, total and free IGF-I levels in serum of normal and STZ-induced diabetic rats were 67.6±36.8, 2.6±2.0 ng/ml and 40.5±28.7, 2.0±0.8ng/ml, respectively. The levels of total and free IGF-I were significantly lower in STZ-induced diabetic rats than normal rats ($p<0.01$).

The levels of total IGF-I in liver and kidney were presented in Fig 2. In liver, the level of total IGF-I was significantly lower ($p<0.01$) in STZ-induced diabetic rats (1.6± 0.3ng/ml) than normal rats (2.1±0.3ng/ml). Whereas, the levels of total IGF-I in kidney was significantly higher ($p<0.01$) in STZ-induced diabetic rats (3.8±0.8ng/ml) than normal rats (2.1±0.6ng/ml).

The patterns of IGFBPs in serum and tissues : The patterns of serum IGFBPs analyzed by WLB were shown in Fig 3. Both of serum in normal and STZ-induced diabetic rats showed 38-42kDa (IGFBP-3), 34kDa (IGFBP-2) and 24kDa (IGFBP-4). The amount of IGFBP-3 in serum from STZ-induced diabetic rats was markedly lower than that of normal rats. But the amount of IGFBP-2 in serum was increased in STZ-induced diabetic rats than normal rats.

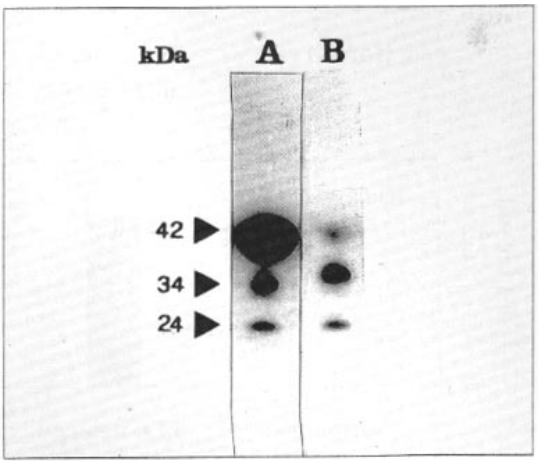

Fig 3. IGFBPs pattern in serum of normal (n = 15) and streptozotocin-induced diabetic rats (n = 15) by western ligand blotting (WLB). After quantitative analysis of protein, pooled samples were analysed by WLB. 10 μl of samples were electrophoresed on 12% SDS-PAGE gel under nonreducing conditions. The proteins were transferred onto nitrocellulose filters, incubated with [^{125}I]-IGF-I, and exposed to X-ray film for 7 days. IGFBPs, insulin-like growth factor binding proteins; Lane A, normal rat serum; Lane B, streptozotocin-induced diabetic rat serum; IGFBP-3, 43kDa; IGFBP-2, 34kDa; IGFBP-4, 24kDa.

The patterns of IGFBPs in liver and kidney from normal and STZ-induced diabetic rats analyzed by WLB were shown Fig 4 and Fig 5. The patterns of IGFBPs in the liver were

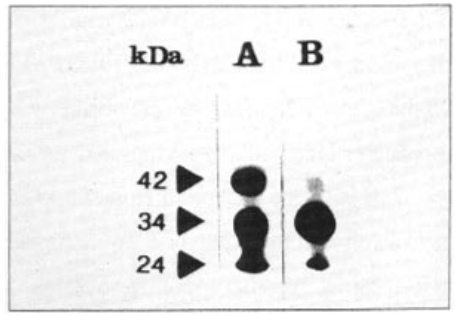

Fig 4. IGFBPs pattern in liver of normal (n = 15) and streptozotocin-induced diabetic rats (n = 15) by western ligand blotting (WLB). After quantitative analysis of protein, pooled samples were analysed by WLB. 10 μl of pooled samples were electrophoresed on 12% SDS-PAGE gel under nonreducing conditions. The proteins were transferred onto nitrocellulose filters, incubated with [^{125}I]-IGF-I, and exposed to X-ray film for 7 days. IGFBPs, insulin-like growth factor binding proteins; Lane A, normal rat liver; Lane B, streptozotocin-induced diabetic rat liver; IGFBP-3, 42kDa; IGFBP-2, 34kDa; IGFBP-4, 24kDa.

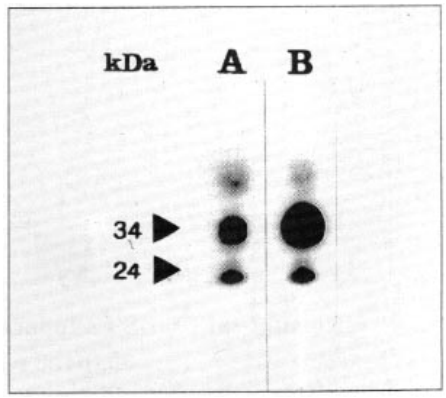

Fig 5. IGFBPs pattern in kidney of normal (n = 15) and streptozotocin-induced diabetic rats (n = 15) by western ligand blotting (WLB). After quantitative analysis of protein, pooled samples were analysed by WLB. 10 μl of pooled samples were electrophoresed on 12% SDS-PAGE gel under nonreducing conditions. The proteins were transferred onto nitrocellulose filters, incubated with [^{125}I]-IGF-I, and exposed to X-ray film for 7 days. IGFBPs, insulin-like growth factor binding proteins; Lane A, normal rat kidney; Lane B, streptozotocin-induced diabetic rat kidney; IGFBP-3, 42kDa; IGFBP-2, 34kDa.

similar to those of serum as follows. The amount of IGFBP-3 in liver was decreased in STZ-induced diabetic rats than normal rats and the amount of IGFBP-2 in liver was increased in STZ-induced diabetic rats than normal rats.

In kidney, there was predominant IGFBP-2 and fainted IGFBP-3 in both of normal rats and STZ-induced diabetic rats. STZ-induced diabetic rats have increased IGFBP-2 than normal rats. There were not different in IGFBP-3 and IGFBP-4 between normal rats and STZ-induced diabetic rats.

The profiles of IGF carrier proteins in serum : The characteristics of serum IGF-I carrier proteins in normal rats and STZ-induced diabetic rats were shown in Fig 6. 150kDa and 50kDa carrier proteins were identified in serum of normal rats and STZ-induced diabetic rats. The serums of normal rats have higher 150kDa carrier protein than in STZ diabetic rats. Whereas, most of 50kDa carrier protein was found in STZ-induced diabetic rats. The levels of free IGF-I were similar in both group.

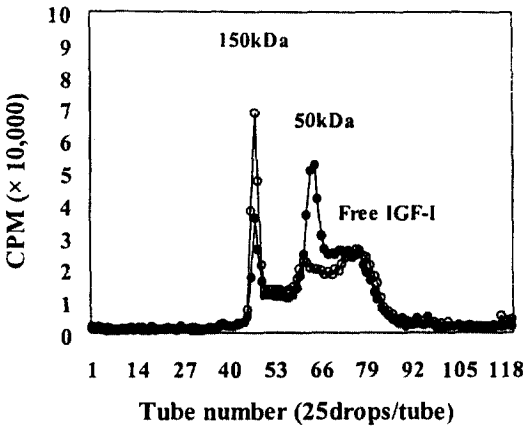

Fig 6. IGF-I carrier protein profiles in serum from normal (○, n = 15) and streptozotocin-induced diabetic rats (●, n = 15) using Sephacryl S-300 column. A mixture of $H_2O/Na_2PO_4/NaH_2PO_4$ was used as the mobile phase. Pooled samples (100 μl) were incubated with [^{125}I]-IGF-I for 18 hours at 4℃ and flow rate was 6ml/hr. CPM ; count per minute.

Discussion

This study was conducted to compare the differences in IGFs/IGFBPs system including levels of total and free IGF-I , patterns of IGFBPs and profiles of IGF carrier proteins in serum and tissues between normal and STZ-induced diabetic rat, and investigate the relationships of IGFs/IGFBPs system between serum and tissues from normal and STZ-induced diabetic rats.

Several studies reported that poor glycemic control in diabetes is associated with reduced serum IGF-I levels[6,7]. Lowered IGF-I levels in the blood may thus result in decreased IGF-I bioavailability at the tissue level[15]. Because IGFBPs suppress IGFs actions in circulate, only the unbound form of IGFs is suggested to be biological active. Therefore, free IGF-I may have greater physiological and clinical relevance than total IGF-I [15]. Our results showed that the levels of total IGF-I as well as free IGF-I in serum were significantly low in STZ-induced diabetic rat. This result that decreased total IGF-I level was agree with above findings and hypothesis[6,7] and decreased free IGF-I level which was not reported previous studies was also might be effect to bioavailability of IGF-I to tissues with diabetes.

The main source of circulating IGF-I is considered to be the liver[16]. Decreased total and free IGF-I level in serum were might due to a decrease of IGF-I production in liver. Luo and Murphy (1991)[17] reveal that decrease in IGF-I mRNA in the liver of diabetic rats. And treatment of diabetic rats with insulin resulted in a small, non significant increase in hepatic IGF-I mRNA. In our results, the level of total IGF-I in liver was significantly low in STZ-induced diabetic rats. These observations are demonstrated that diminished IGF-I m RNA expression resulted in decreased IGF-I production in liver, and then finally, it induced decreased IGF-I level in serum.

However, in contrast to decrease of IGF-I level in liver, there was a significant increase of IGF-I level in kidney from STZ-induced diabetic rat. Phillip *et al*[18] suggest that the transient accumulation of IGF-I in the kidney of STZ-diabetic rat may not be due to an increase in the local synthesis of IGF-I , but rather to an increase in IGF-I uptake from the circulation due to non-membrane-associated IGFBPs. In our results of IGFBPs pattern, amount of IGFBP-2 in kidney was increased in STZ-induced diabetic rats. Therefore.

this changes of IGFBPs, especially increased amount of IGFBP-2 is may associate with increased IGF-Ⅰ in kidney. Also recent studies have shown that the renal synthesis of IGFBPs is altered in diabetes, suggesting that these changes may be implicated in alterations in renal functions and morphology that accompany diabetes. Since we did not determine the indices involved in renal functions in our study, further work is necessary to determine the relation with IGFs/IGFBPs system and renal functions.

The changes of IGFBPs patterns in serum and liver were analyzed by WLB. The amount of IGFBP-3 was markedly decreased in serum and liver, the amount of IGFBP-2 was increased in liver, and the amount of IGFBP-4 were not change in serum and liver from STZ-induced diabetic rats. These our results were partially explained by Luo *et al*[19] 's findings. Luo *et al*[19] showed a significant increase in the amount of hepatic IGFBP-1 and IGFBP-2 mRNA was seen 1 month and 3 months after onset of diabetes. In contrast to the increase in hepatic IGFBP-1 and IGFBP-2 mRNA, a significant decrease in hepatic IGFBP-3 mRNA (54.6% of control, $p<0.0005$ and 64.6% of control, $p<0.005$ for 1 and 3 months, respectively), and no significant difference in hepatic IGFBP-4 mRNA levels were seen in diabetic rats. Therefore, it may suggest that change of serum IGFBP-3 in our study was due to change of hepatic IGFBP-3 pattern, and this change may be regulated at the transcriptional level.

Whereas most circulating IGF-Ⅰ present in 150kDa complex containing IGFBP-3 and acid labile subunit (ALS), a partial 50kDa exist containing IGFBP-1, IGFBP-2, and IGFBP-4 in blood[20,21]. The 150kDa complex serves as a potential reservoir and increases their circulating half-lives and suppresses their hypoglycemic potential[22,23]. Also, the 50 kDa complex are capable crossing the biological membrane, but 150kDa complex are not. Its profiles were changed by catabolic stress such as surgery, disease state, and pregnancy[24]. In our study, STZ-induced diabetic rats have significantly decreased 150kDa carrier protein and increased 50kDa carrier proteins. These results were may explain that decreased 150kDa carrier protein was result in decreased IGF-Ⅰ level and amount of IGFBP-3 in serum and tissue. Therefore, changes of IGF-Ⅰ carrier protein profiles in serum may be affect the prolonging IGF-Ⅰ half-lives, bioavailability of IGF-Ⅰ to tissue, and glycemic control in diabetes.

In conclusion, these results demonstrate that in STZ-induced diabetic rats, IGF-Ⅰ/IGFBPs system that included functional bioactivity was changed in serum as well as tissues, and these changes may play an important role in pathogenesis of diabetes.

References

1. Froesch ER, Schmid C, Schwander J, *et al*. Actions of insulin-like growth factors. *Annu Rev Physiol*, 47:443-467, 1985.
2. Humbel RE. Insulin-like growth factors Ⅰ and Ⅱ. *Eur J Biochem*, 190:445-462, 1990.
3. Cohen P, Rosenfeld RG. Physiologic and clinical relevance of the insulin-like growth factor binding proteins. *Curr Opin Pediatr*, 6:462-467, 1994.
4. Carroll PV, Umpleby M, Alexander EL, *et al*. Recombinant human insulin-like growth factor-Ⅰ (rhIGF-Ⅰ) therapy in adults with type 1 diabetes mellitus; effects on IGFs, IGF-binding proteins, glucose levels and insulin treatment. *Clin Endocrinol*, 49:739-746, 1998.
5. Kostecka Y, Blahovee J. Insulin-like growth factor binding proteins and their functions (minireview). *Endocr Regul*, 33:90-94, 1999.
6. Moxley Ⅲ RT, Arner P, Moss A, *et al*. Acute effects of insulin-like growth factor Ⅰ and insulin on glucose metabolism *in vivo*. *Am J Phsiol*, 259:E561-E567, 1990.
7. Spagnoli A, Chiarelli F, Vorwerk P, *et al*. Evaluation of the components of insulin-like growth factor (IGF)-IGF binding protein (IGFBP) system in adolescents with type Ⅰ diabetes and persistent microalbuminuria: relationship with increased urinary excretion of IGFBP-3 18 kDa N-terminal fragment. *Clin Endocrinol*, 51:587-596, 1999.
8. Hasegawa T, Hasegawa Y, Takada M, *et al*. Insulin-like growth factors-insulin-like growth factor binding protein axis and diabetic control in insulin-dependent diabetes mellitus. *Endocr J*, 45:s129-131, 1998.
9. Miyatake N, Shikata K, Wada J, *et al*. Differential dis-

tribution of insulin-like growth factor- I and insulin like growth factor binding proteins in experimental diabetic rat kidney. *Nephron*, 81:317-323, 1999.

10. Sara VR, Hall K. Insulin-like growth factors and their binding proteins. *Physiol Rev*, 70:591-614, 1990.
11. Goya L, Rivero F, Martin MA, *et al*. Liver mRNA expression of IGF- I in adult undernourished diabetic rats. *Life Science*, 64:2255-2271, 1999.
12. Lee CY, Henricks DM. Comparisions of various acidic treatments of bovine serum on insulin-like growth factor- I immunoreactive and binding activity. *J Endocrinol*, 127:139-148, 1990.
13. Lee DY, Kang CW, Kim JS. Ca^{2+} effects on synthesis and secretion of insulin-like growth factor(IGF- I) and IGF-binding proteins by the perfused rat liver. *J Kor Soc Endocrinol*, 11:189-198, 1996.
14. Hossenlopp P, Seurin D, Segovia-Quinson B, *et al*. Analysis of serum insulin-like growth factor binding proteins using western blotting : use of the method for titration of the binding proteins and competitive binding studies. *Anal Biochem*, 154:138-143, 1986.
15. Janssen JA, Jacobs ML, Derkx FH, *et al*. Free and total insulin-like growth factor I (IGF- I), IGF-binding protein-1 (IGFBP-1) and IGFBP-3 and their relationships to the presence of diabetic retinopathy and glomerular hyperfiltration in insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab*, 82:2809-2815, 1997.
16. Rosen CJ, Pollak M. Circulating IGF- I : New perspectives for a new century. *TEM*, 10:136-141, 1999.
17. Leu JM, Murphy LJ. Differential expression of insulin-like growth factor- I and insulin-growth factor binding protein-1 in the diabetic rat. *Mol Cell Biochem*, 103:41-50, 1991.
18. Phillip M, Werner H, Palese T, *et al*. Differential accumulation of insulin-like growth factor- I in kidneys of pre- and postpubertal streptozotocin-diabetic rats. *J Mol Endocrinol*, 12:215-224, 1994.
19. Leu JM, Murphy LJ. Differential expression of insulin-like growth factor- I and insulin-growth factor binding protein-1 in spontaneously diabetic rat. *J Mol Endocrinol*, 8:155-163, 1992.
20. Nisseley SP. The serum half-life of somatomedin activity ; evidence for growth hormone dependence. *ACTA Endocrinol*, 83:243-258, 1976.
21. Conover CA, Ronk M, Lombana F, *et al*. Structural and biological chracterization of bovine insulin-like growth factor binding-3. *Endocrinol*, 127:2795-2803, 1990.
22. Lee CY, Rechler MM. Proteolysis of insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) in 150-kilodalton IGFBP complexes by a cation-dependent protease activity in adult rat serum promotes the release of bound IGF- I . *Endocrinol*, 137:2051-2058, 1996.
23. Rhoads RP, Greenwood PL, Bell AW, *et al*. Organization and regulation of the gene codding the sheep acid-labile subunit of the 150 kilodalton insulin-like growth factor-binding protein complex. *Endocrinol*, 141:1425-1433, 2000.
24. Jones JL, Clemmons DR. Insulin-like growth factors and their binding proteins ; biological actions. *Endocrinol*, 16:3-33, 1995.

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Streptozotocin에 의해 유도된 당뇨쥐의 IGF-I, IGFBPs 및 IGF-I carrier protein의 변화

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(2000년 8월 7일 게재승인)

국문초록 : 본 연구에서는 Streptozotocin-induced 당뇨가 혈청과 간장 및 신장조직의 IGF-I, IGFBPs 및 IGF-I carrier protein 특성에 미치는 영향을 조사하였다. 혈액과 조직중의 IGF-I 농도는 방사면역측정법으로 측정하였고, IGFBPs 양상은 Western Ligand Blotting(WLB)으로 관찰하였으며, IGF-I carrier protein의 특성은 column chromatography로 측정하였다. 혈청과 IGF-I 농도는 당뇨군이 대조군에 비하여 유의하게 감소하였다($p<0.01$). 당뇨군은 대조군에 비하여 간장 IGF-I 농도는 유의하게 감소한 반면, 신장의 IGF-I 농도는 유의하게 증가하였다($p<0.01$). 당뇨군은 대조군에 비하여 혈청과 간장의 IGFBP-3는 감소한 반면, IGFBP-2는 증가하였고, IGFBP-4는 변화가 없었다. 또한 당뇨군은 대조군에 비하여 150kDa carrier protein은 감소하였으며, 50kDa carrier protein은 증가하였다. 이상의 결과를 종합해볼 때 Streptozotocin-induced 당뇨는 혈청 뿐만 아니라 조직의 IGF-I/IGFBP system 변동에 영향을 미침을 알 수 있었다.

Key words : IGF-Ⅰ, IGFBPs, IGF-Ⅰ carrier proteins, diabetes.