The effect of mosapride (5HT-4 receptor agonist) on insulin sensitivity in subjects with impaired glucose tolerance

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The effect of mosapride (5HT-4 receptor agonist) on insulin sensitivity in subjects with impaired glucose tolerance

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ABSTRACT

The effect of mosapride (5HT-4 receptor agonist) on insulin sensitivity in subjects with impaired glucose tolerance

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Mosapride, a widely used prokinetic agent for the patients with non-ulcer dyspepsia, diabetic gastroparesis, or reflux esophagitis, enhances gastric emptying by the mechanism of the agonist action at serotonin 5-HT 4 (5-hydroxytryptamine) receptors and facilitation of cholinergic excitatory neurotransmission. Previous clinical study showed that mosapride is effective in decreasing plasma glucose concentrations without stimulating insulin secretion in type II diabetic patients. We investigated the effect of mosapride on blood glucose and insulin concentration in subjects with impaired glucose tolerance. To evaluate the mechanism of mosapride, we used human skeletal muscle cells in primary culture and in these cultured myotubes, we assessed insulin-induced GLUT-4 (glucose transporter 4) translocation and tyrosine phosphorylation of IRS-1 (insulin receptor substrate-1). Thirty subjects with impaired glucose tolerance were randomly assigned to receive either mosapride (5mg orally three times a day, n=20) or a placebo (n=10) for 2 weeks. Changes in blood glucose and insulin concentrations were determined basally as well as after mosapride treatment. Insulin sensitivity was evaluated during euglycemic hyperinsulinemic clamp test. After 2 weeks treatment of mosapride in subjects with IGT follow-up glucose disposal rates were higher than initial values, and were significantly increased to those of control

(mosapride 5.47 ± 1.72 vs 7.06 ± 2.13 p=0.004, placebo 5.42 ± 1.85 vs 5.23 ± 1.53 $mg.kg^{-1}.min^{-1}$). Fasting plasma glucose and insulin levels were decreased. But other metabolic parameters such as blood pressure, total cholesterol, triglyceride and HDL-cholesterol were not improved. In primary cultured human skeletal muscle cell, GLUT-4 expression and tyrosine phosphorylation of IRS-1 is measured using SDS-PAGE and immunoblotting method. Mosapride increased contents of GLUT4 in the plasma membrane that occurs as result of the increased recruitment of glucose transporters from an intracellular pool to the cell surface. Treatment of human skeletal muscle cell with insulin resulted in tyrosine phosphorylation of IRS-1. In contrast, mosapride did not increase tyrosine phosphorylation of IRS-1. The present results indicate that 5 HT-4 receptor agonist is effective in decreasing plasma blood glucose concentration without stimulating insulin secretion in IGT subjects and its mechanism is potentially stimulation of GLUT4 translocation in skeletal muscle.

Key words : 5 HT-4 receptor, Euglycemic hyperinsulinemic clamp, GLUT-4, IRS-1

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I. INTRODUCTION

Insulin resistance is a key feature of impaired glucose tolerance (IGT) and type 2 diabetes.[1] It is characterized by a diminished ability of insulin-sensitive tissues to take up and metabolize glucose in response to insulin. Skeletal muscle is the primary site of insulin-mediated glucose disposal and contributes significantly to decreased glucose uptake, as seen in states of insulin resistance.[2] Defects in the early insulin-signaling cascade leading to glucose uptake have been shown to play a key role in the pathogenesis of insulin resistance.[3] In target tissues, such as skeletal muscle, insulin promotes glucose uptake through the translocation of the GLUT4 (glucose transporter 4) from an intracellular vesicular pool to the plasma membrane. Insulin binding to the extracellular α-subunit of its receptor results in autophosphorylation of tyrosine residues in the receptor ß-subunit and activation of a tyrosine kinase intrinsic to the ß-subunit. This leads to the recruitment and tyrosine phosphorylation of intracellular substrates such as insulin receptor substrates (IRSs) 1–4. Phosphotyrosines on the IRS proteins bind the p85 regulatory subunit of phosphatidylinositol 3' (PI3) kinase. PI3 kinase is a heterodimer of a regulatory subunit (p85) and a catalytic subunit

(p110), and its activation in response to insulin results primarily through its association with the IRS proteins.[4]

Mosapride, a widely used prokinetic agent for the patients with non-ulcer dyspepsia, diabetic gastroparesis, or reflux esophagitis, enhances gastric emptying by the mechanism of the agonist action at serotonin 5HT-4 receptors and facilitation of cholinergic excitatory neurotransmission.[5] Ueno et al. reported mosapride improved insulin action at muscle and glycemic control in type 2 diabetic patients.[6]

Serotonin, also known as 5-hydroxytryptamine (5HT), is a neurotransmitter that has been implicated in the regulation of diverse physiological processes, including cellular growth and differentiation,[7] neuronal development,[8] and regulation of blood glucose concentration.[9,10] Recent work showing that rat fetal myoblasts express the 5HT-2A receptor [11] and that activation of this receptor enhances the expression of genes associated with myogenic differentiation and that of the fetal glucose transporter, GLUT3.[11]

The first aim of this study was to examine the effect of mosapride, 5 HT-4 receptor agonist on insulin sensitivity of the subjects with impaired glucose tolerance by euglycemic hyperinsulinemic clamp test. The second aim of this study was to elucidate the mechanism to improve insulin sensitivity of mosapride, 5 HT-4 receptor agonist using human muscle cell *in vitro*.

II. MATERIALS AND METHODS

1. Subjects

Thirty subjects with impaired glucose tolerance (fasting plasma glucose levles of 100 - 125 mg/dl and/or plasma glucose levels between 141 and 199 mg/dl at 2 hrs standard oral glucose tolerance test (75g glucose loading)) were participate in these studies. Informed consent was obtained from all subjects after explanation of the protocol. No subject was taking pharmacological agents known to affect carbohydrate metabolism. Participants were also instructed not to alter body weight or lifestyle habits (eating, drinking, smoking, and exercise) during their participation in the study. After the baseline studies, twenty subjects took moasapride (5 mg t.i.d daily p.o. Daewoong pharmacentical, Seoul, Korea) for 2 weeks. The remaining ten subjects took placebo for 2 weeks. Blood samples and clamp test were taken before and after mosapride treatment.

2. Anthropometric parameters & biochemical profiles

Body weight and height were measured in the morning, without clothing and shoes. BMI was calculated as body weight in kilograms divided by height in meters squared (kg/m^2).

Serum glucose was measured immediately by an autoanalyzer using the hexokinase method (Roche, Hitachi 747). Serum insulin and c-peptide were determined by an enzyme chemiluminescence immunoassay (ECIA, DPC, Immulite 2000). Serum total cholesterol, HDL-cholesterol and LDL-cholesterol were assessed by the enzymatic methods (Daiichi, Hitachi 747) and serum triglycerides were measured by the enzymatic colorimetric methods (Roche, Hitachi 747).

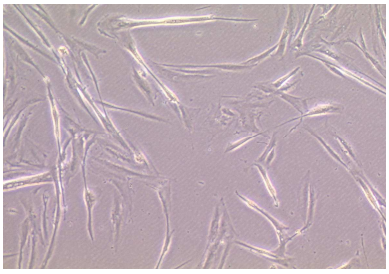
3. Euglycemin hyperinsulinemic clamp test

Insulin sensitivity was measured during euglycemic hyperinsulinemic clamp test. After a 10- to 12-h overnight fast, subjects were admitted to the outpatient clinic at 8:00 A.m. A polyethylene cannula was inserted into an antecubital vein for the infusion of all test substances. A second catheter was inserted retrogradely into an ipsilateral wrist vein on the dorsum of the hand for blood sampling, and the hand was kept in a heated box at 65 deg C. Squared priming was performed (0–9 min) with a stepwise decline in the insulin (Humalog, lilly, U.S.A) infusion rate every third minute, thereby reducing the insulin infusion rate from 100–80 to 60–40 mU $\cdot$ m^{-2} $\cdot$ min^{-1}. Thereafter, the insulin infusion rate was fixed at 40 mU $\cdot$ m^{-2} $\cdot$ min^{-1} from 9 to 120 min.

During the last 30 min of the basal equilibration period, plasma samples were taken at 5- to 10-min intervals for determination of plasma glucose and insulin concentrations. The plasma glucose concentration was measured every 5 min after the start of the insulin infusion, and a variable infusion of 20% glucose was adjusted based on the negative feedback principle to maintain the plasma glucose level at 90 mg/dl with a coefficient of variation <5%. Plasma samples were collected every 15 min from 0 to 90 min and every 5-10 min from 90 to 120 min for determination of plasma glucose and insulin concentrations. Plasma glucose concentration was maintained constant at euglycemia, using a variable glucose infusion (180 g/l).[12] Plasma glucose concentration was monitored every 5 min using an automated glucose oxidase method (Glucose Analyzer 2, Beckman Instruments, Fullerton, CA).

4. Material and primary human cell culture.

Human muscle cells were provided by Professor Yoon Ghil Park (Muscular disease research center, Yongdong severance hospital, Seoul, Korea) and primary cultured as previously described.[13] Cells were grown at 37℃, in an incubator containing 5%CO_2 incubator. They were then fused for 4 days in DMEM medium, 20% Fetal Bovine Serum, 1% penicillin, streptomycin. In culture, after differentiation, most of human skeletal muscle myoblasts fused into multinucleated myotubes, as shown in Figure 1. Immunostaining was performed with an antibody against human sarcomeric actin, which is expressed in differentiated skeletal muscle.



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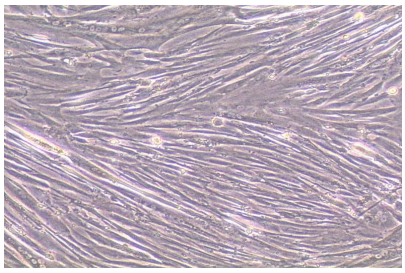

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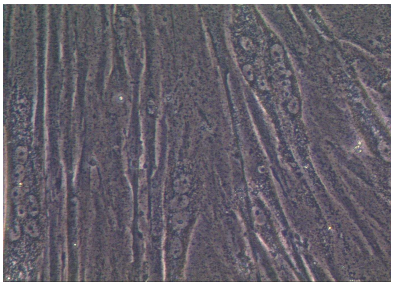

C.

Figure 1. Photomicrographs of myoblasts from primary culture of human skeletal muscle cell. A and B show myoblasts during the growing phase.

When the cells were almost confluent, they were changed to differentiation media, and most of these myoblasts fused to multinucleated myotubes(C.)

5. Glucose transporter in human skeletal muscle

Human skeletal muscle cells were exposed to insulin, or mosapride for 1-4 hours and for 10^{-7} to 10^{-9} concentrations. Subcellular fractionation of human skeletal muscle membranes, i.e plasma, and intracellular membranes were prepared from muscle cells as described previously.[14] Isolated membrane fractions from human skeletal muscle cell were subjected to SDS-PAGE on 8% resolving gels and immunoblotted as previously reported (30ug protein, 5 % silk milking blocking 1 hr).[14] Protein content of each of the isolated membrane fractions was determined using the BCA protein assay kit. Nitrocellulose membranes were probed with antisera against GLUT4 (1:2000, abcam, M.A, U.S.A). Primary antibody detection was performed using either horseradish peroxidase-conjugated anti-rabbit IgG (1:2000, SAPU, Scotland) or anti-mouse (1:2000, SAPU, Scotland) for 1 h.

6. IRS-1 tyrosine phosphorylation

Myotubes were starves overnight and stimulates with 17 nmol/l insulin for 3, 10, 15, 30 , and 60 min. Cells were lysed, IRS-1 were immunoprecipitated with specific antibodies (1:100, Upstate Biotechnology Inc., lake Placid, NY, U.S.A.) and then separated by SDS-PAGE. After transfer, membrane were first probed with an anti-phosphotyrosine antibody and then stripped and probed with an anti IRS-1 antibody (Upstate Biotechnology Inc., lake Placid, NY, U.S.A.).

7.Statistical analyses

All statistical analyses were performed using SPSS Win 11.0 (Statistical Package for Social Science, SPSS, Chicago, II, USA.). All data are presented

as means ± SD. Pre- to post therapy values are compared using a paired t test, with significance reached at $P < 0.05$.

III. RESULTS

1. *In vivo* study

Clinical characteristics of subjects are given in Table 1. The subjects were matched for age. Basal blood glucose values, other anthropometric parameters and biochemical profiles were comparable between two groups. Treatment of mosapride to IGT patients improves glucose utilisation (mosapride 5.47 ± 1.72 vs 7.06 ± 2.13, p=0.004 , placebo 5.42 ± 1.85 vs 5.23 ± 1.53 $mg.kg^{-1}.min^{-1}$) in euglycemic hyperinsulinemic clamp test. Glycemic control was improved: significant decreases were observed in the concentrations of fasting blood glucese (115.2 ± 21.3 vs 107.11± 15.3 mg/dl , p<0.005) after 2 weeks of treatment of mosapride (Table 1&2, Figure 2).

Table 1. Baseline clinical characteristics

	Mosapride group	Control group
N	20	10
Sex (male/female)	14/6	8/2
Age (years)	50 ± 11	48 ± 9
BMI (kg/m^2)	25.3 ± 1.7	25.8 ± 1.2
Systolic BP (mmHg)	120 ± 3	120 ± 2
Diastolic BP (mmHg)	79 ± 2	80 ± 1
Current Smoking (%)	25	30

Values are expressed as means ± SD, N: number, BMI: body mass index, BP: blood pressure

Tabe.2. Effect of mosapride on metabolic parameters in study subjects.

	Mosapride group (N=20)		Control group (N=10)	
	baseline	2 weeks	baseline	2 weeks
BMI (kg/m^2)	25.3 ± 1.7	25.2 ± 1.5	25.8 ± 1.2	25.8 ± 0.9
Systolic BP (mmHg)	120 ± 3	121 ± 1	120 ± 2	122 ± 4
Diastolic BP (mmHg)	79 ± 2	80 ± 1	80 ± 1	78 ± 1
Fasting glucose (mg/dl)	115.2 ± 21.3	107.11± 15.3*	114.2 ± 20.9	113.9 ± 19.2
HbA1c (%)	5.58 ± 0.6	5.4 ± 0.5	5.59 ± 2.2	5.55 ± 1.2
Total cholesterol (mg/dl)	176 ± 28	179 ± 34	172 ± 25	179 ± 29
Triglyceride (mg/dl)	143 ± 101	156 ± 74	149 ± 82	162 ± 75
HDL-cholesterol (mg/dl)	38 ± 5	39 ± 9	39 ± 9	37 ± 5
LDL-cholesterol (mg/dl)	112 ± 20	109 ± 29	115 ± 15	118 ± 19
Fasting insulin (μU/ml)	5.30 ± 3.0	4.81 ± 2.8*	5.28 ± 2.6	5.30 ± 3.2
Fasting C-peptide (ng/ml)	2.07 ± 0.32	1.98 ± 0.50	2.01 ± 0.24	2.07 ± 0.42
GDR ($mg.kg^{-1}.min^{-1}$)	5.47 ± 1.72	7.06 ± 2.13*	5.42 ± 1.85	5.23 ± 1.53

Values are expressed as means ± SD , * $P<0.05$ from baseline. N: number, BMI: body mass index, BP: blood pressure, GDR: glucose disposal rate

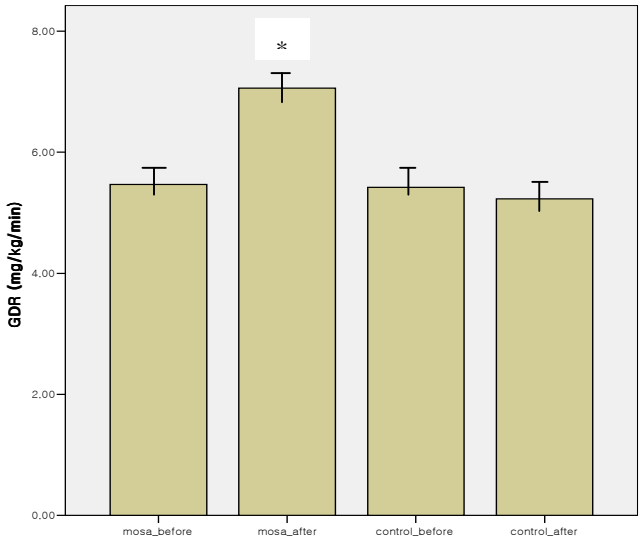

Figure 2. The change of glucose disposal rate during euglycemic hyperinsulinemic clamp test.

* P<0.05 from baseline, GDR ($mg.kg^{-1}.min^{-1}$)

Mosa_before: mosapride treatment group, 0week, mosa_after: mosapride treatment group, 2weeks after medication, control_before:placebo group,0week, control_after:placebo group, 2weeks after medication

2. GLUT-4 expression

To examine the mechanism of 5 HT-4 receptor agonist to improve insulin sensitivity, we compare protein expression GLUT-4 and IRS-1 with specific antibodies directed against these proteins between muscle cells treated with insulin and mosapride. Figure 3 shows representative immunoblots from separate experiments showing that mosapride induces an increase in the plasma membrane abundance of GLUT-4. To gain some insight into whether components of the insulin signaling pathway may participate in 5-HT4 receptor signaling we investigated whether mosapride

treatment modulated the phosphorylation status of IRS.

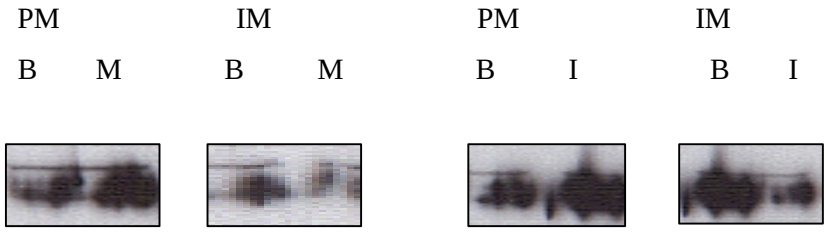

Figure 3. Effect of insulin and mosapride on the abundance of GLUT4 in subcellular membrane fractions from human muscle cell. PM:Plasma membrane, IM:Intracellular membrane, B:basal, I:Insulin, M:mosapride

3. IRS-1 tyrosine phosphorylation

IRS-1 are phosphorylated on tyrosine residues by the insulin receptor after insulin stimulation. Figure 5 shows an anti-phosphotyrosine blot of IRS-1 immunoprecipitates. Insulin induced tyrosine phosphorylation of IRS-1 but mosapride did not. This result suggested that IRS-1 was not a downstream target for 5HT-4 receptor.

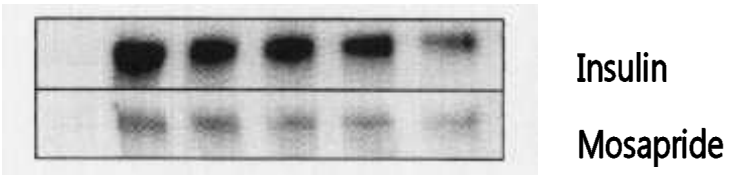

Figure 4. IRS-1 tyrosine phosphorylation. Myotubes were starved overnight and then stimulated with insulin (17nmol/l, upperline) and mosapride(lower line).

IV.DISCUSSION

The course of type 2 diabetes is slow and metabolic abnormalities that lead to hyperglycemia are established long before overt diabetes (as defined by World Health Organization/American Diabetes Association criteriae[15-17]) developes.[17-19] This state, where abnormalities in glucose metabolism are present but elevation in glucose is below the cutoff point for establishing the diagnosis of type 2 diabetes, is referred to as pre-diabetes.[20] Insulin resistance is also major pathophysiology of IGT state as over type 2 diabetes. Skeletal muscle is the major organ for insulin-stimulated glucose disposal[21] and glucose transport is rate limiting for such disposal. [2] Before over diabetic stage, impaired activation of glucose transport in muscle contributes importantly to insulin resistance in type 2 diabetes, [2] in both later and earlier phases, including impaired glucose tolerance, wherein blood glucose levels are only minimally increased.

Defects in the insulin-signaling cascade leading to GLUT4 translocation and glucose uptake play an important role in the pathogenesis of insulin resistance in skeletal muscle.[2,22] Most of the data have been gathered in patients with full-blown type 2 diabetes. However, little is known regarding signaling defects in prediabetic stages such as IGT.

The mechanisms underlying defects in insulin-stimulated glucose transport in IGT and type 2 diabetes are uncertain. Except for morbid obesity, insulin-sensitive GLUT4 glucose transporter levels in skeletal muscle are not altered[23] and further studies have suggested that there may be defects in insulin signaling and translocation of glucose transporters to the plasma membrane.

Previous work has shown that mosapride treatment led to a reduction in hyperglycemia with a simultaneous reduction in circulating insulin secretion of the patients with type 2 DM.[6] They also have shown that there expressed 5 HT-4 receptors in the muscle as well as in the brain and intestine by RT-PCR analysis. In the present group of IGT patients after 2 weeks of mosapride treatment, the simultaneous fall in blood glucose and insulin concentration suggested an overall improvement in insulin action. This was clearly shown in the increase glucose utilization in the euglycemic hyperinsulinemic clamp test.

In these studies the resulting hypoglycemia could not explained by an increase in insulin secretion and proposed that potential mechanism by which 5HT-4 receptor agonist may promote a lowering blood glucose was directly stimulating glucose uptake in skeletal muscle; a notion based on recent work showing that human skeletal muscle express the 5HT-4 receptor.[6] To test this hypothesis we carried out SDS-PAGE and immunoblotting to determine increase of translocation of GLUT4 from internal membrane to plasma membrane after mosapride treatment. To gain some insight into whether components of the insulin signaling pathway may participate in 5HT-4 receptor signaling, we investigated whether 5HT-4 receptor stimulation modulate the phosphorylation status of IRS-1. IRS-1 tyrosine phosphorylation has a tendency to be lower in mosapride treated cell. This result suggested that 5HT-4 receptor agonist causes a rapid stimulation in glucose transport that occurs as a result of the increased recruitment of glucose transporters ftom an intracellular pool to the cell surface. Post-receptor signaling events involved in eliciting this stimulation currently unknown.

Recent studies suggest that insulin stimulates glucose transport through insulin receptor-mediated tyrosine phosphorylation of IRS-1 or other intermediates that activate PI3K, which, through increases in PI-3,4,5-$(PO_4)_3$

(PIP $_3$), activate downstream effectors protein kinase B (PKB/Akt) [24-27] and atypical protein kinase Cs (aPKCs) ζ and λ/ι.[28-32] Although defects in IRS-1-dependent PI 3-kinase activation by insulin in muscle of type 2 diabetic human subjects have been reported,[33-35] information on downstream activators of glucose transport is controversial or lacking. Thus, defective PKB activation was seen during incubation of muscle strips of nonobese type 2 diabetic humans,[34] whereas PKB activation was undiminished in muscle biopsies taken during clamp studies in obese type 2 diabetic humans.[35] Further, it is currently unknown whether aPKC activation is defective in muscles of type 2 diabetic subjects.

Concerning IGT, decreased incremental but normal absolute levels of IRS-1-dependent PI3K and no significant reduction in PKB phosphorylation were seen in human muscle in a eyglycemic hyperinsulinemic clamp test,[36] suggesting that other factors may contribute more directly to defects in insulin-stimulated glucose disposal. On the other hand, defects in glucose transport and IRS-2-dependent PI 3K and aPKC activation were observed in cultured myocytes obtained from obese/impaired glucose tolerant humans.[37]

V.CONCLUSION

In summary, these results show that 5HT-4 receptor agonist, mosapride is effective in decreasing plasma glucose concentrations without stimulating insulin secretion in IGT patients and 5HT-4 receptor agonist causes a rapid stimulation in glucose transport that occurs as a result of the increased recruitment of glucose transporters from an intracellular pool to the cell surface.

The result that IRS-1 tyrosine phosphorylation has a tendency to be lower in mosapreide treated cell indicated that 5HT-4 receptor agonist can stimulate translocation of GLUT4 in skeletal muscle by a mechanism of which does not depend upon components that participate in the early insulin signaling pathway.

Further study should focus on activation of PI3K (phophoinositide 3-kinase) with treatment of mosapride and possibility that 5HT-4 receptor signaling may converge at some point downstream of PI3K.

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< 국문요약 >

내당능장애자에서 mosapride(5HT-4 효현제)의 2 주간 투여가 인슐린 감수성에 미치는 영향

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Mosapride 는 소화관 운동장애 시에 소화관 운동 촉진제로 널리 사용되어 지고 있는 약제이다. 최근 mosapride 를 일본인 제 2 형 당뇨병 환자에게 투여하였을 때 공복혈당이 감소하고 인슐린 저항성이 개선되었다는 보고가 있다. 본 연구는 내당능 장애환자로 제 2 형 당뇨병의 위험도가 큰 당뇨병 전단계 환자에서 5HT-4 수용체 효현제인 mosapride 를 투여하였을 때 내당능 장애 환자의 공복 혈당과 인슐린 저항성 개선 여부를 알아보고 mosapride 가 인슐린 저항성을 개선시키는 기전을 알아보고자 하였다.

Mosapride 투여군 20 명, 위약군 10 명을 선정하여 mosapride 5mg 을 하루 3 차례 경구 투여하기를 2 주 동안 하였다. 이 때 약물 투여 전과 투여 2 주 후 신체계측 및 생화학적 검사를 시행하고 정상혈당 클램프 검사(euglycemic hyperinsulinemic clamp test)를 시행하였다.

또한, 일차 배양한 인간 골격근 세포에서 SDS-PAGE 와 Immunoblotting 방법을 사용하여 인슐린과 mosapride 를 처치 하였을 때 포도당수송체-4 의 발현의 차이를 관찰하였다. 인슐린 신호 전달 체계에서 어떤 부위가 5HT-4 수용체 신호와 연관 되는지를 알아보기 위하여 인슐린수용체 기질-1 의 인산화가 mosapride 로 처치 하였을 때 증가하는 지를 관찰하였다.

약물 투여 전 두 군간의 나이, 성별, 체 질량 지수, 혈압, 총 콜레스테롤, 중성지방, HDL 콜레스테롤, LDL 콜레스테롤의 차이는 없었다. 2 주간 약물 투여 후 투여 군에서 투여전과 비교하여 공복혈당 (115.2 ± 21.3 vs. 107.11± 15.3 mg/dL, $P<0.05$), 공복 인슐린 (5.30 ± 3.0 vs. 4.81 ± 2.8 μIU/mL, $P<0.05$)이 의미있게 감소하였으며, 정상 혈당 클램프 검사에서 얻은 인슐린 감수성의 지표인 glucose disposal rate 의 상승(5.47 ± 1.72 에서 7.06 ± 2.13 $mg.kg^{-1}.min^{-1}$, $P<0.05$)이 관찰되어 인슐린 저항성이 개선 되었음을 알 수 있었다.

Mosaprede 를 처치한 골격근세포에서 인슐린으로 자극하였을 때 포도당수송체-4 의 세포막으로의 전위(translocation)가 증가됨을 관찰할 수 있었는데 이것을 mosapride 의 인슐린 저항성 개선 기전으로 유추 할 수 있겠다. 인슐린 신호 전달 체계에서 어떤 부위가 5HT-4 수용체 신호와 연관 되는지를 알아보기 위하여 인슐린수용체 기질-1 의 인산화가 mosapride 로 처치 하였을 때 증가하는 지를 SDS-PAGE 와 immunmonoblotting 방법을 이용하여 관찰하였으나 인슐린만 처치 한 골격근 세포와 비교하였을 때 오히려 감소 되는 것으로 나타났다.

본 연구에서 내당능 장애 환자에서 mosapride 를 경구로 투여하였을 때 공복혈당이 의미있게 감소하였고 이 때 C-peptide

의 증가가 동반되지 않은 것으로 보아, 췌장의 베타 세포를 자극하지 않은 상태에서 당 대사를 개선 시켰음을 알 수 있다. 췌장에서 인슐린 분비의 증가 없이 인슐린 저항성의 개선을 통해 당 대사를 호전 시켰음을 알 수 있고 인슐린 저항성의 개선은 정상 혈당 클램프 검사를 통해 확인 할 수 있었다. Mosapride 의 인슐린 저항성 개선 기전은 아직 밝혀진 바가 없는데, 기존의 문헌을 통해 인간의 골격근에 5HT-4 수용체가 존재한다는 것이 알려져 있다. 본 연구에서도 인간 골격근에 mosapride 를 처치 하였을 때 인슐린으로 자극한 경우 포도당수송체-4 가 세포막으로 이동이 증가함을 확인 할 수 있었다. 그러나, 인슐린수용체 기질-1 의 인산화는 오히려 인슐린만 처치 한 경우보다 감소하여 mosapride 의 포도당수송체-4 가 세포막으로 전위를 증가시키는 기전이 세포내 인슐린 신호 전달체계의 초기 신호 단계와는 무관할 것으로 생각할 수 있겠다. 인슐린 신호전달의 마지막 단계인 수송체-4 의 전위를 유도하는데 중요한 역할을 하는 PI3-kinase 의 활성화 여부, 이 후 단계로 알려져 있는 AKt/atypical protein kinase C (ζ/λ)의 자극 여부 등 가능한 기전에 관한 연구가 mosapride 의 인슐린 저항성 개선 기전을 밝히는데 더 필요하겠다.

핵심되는 말 : 5 HT-4 수용체, 정상혈당클램프검사, 포도당수송체-4, 인슐린수용체 기질 -1

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