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Influence of PPAR-α Agonist Fenofibrate on Insulin Sensitivity and Selected Adipose Tissue-derived Hormones in Obese Women with Type 2 Diabetes

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Summary

PPAR-α agonists improve insulin sensitivity in rodent models of obesity/insulin resistance, but their effects on insulin sensitivity in humans are less clear. We measured insulin sensitivity by hyperinsulinemic-isoglycemic clamp in 10 obese females with type 2 diabetes before and after three months of treatment with PPAR-α agonist fenofibrate and studied the possible role of the changes in endocrine function of adipose tissue in the metabolic effects of fenofibrate. At baseline, body mass index, serum glucose, triglycerides, glycated hemoglobin and atherogenic index were significantly elevated in obese women with type 2 diabetes, while serum HDL cholesterol and adiponectin concentrations were significantly lower than in the control group (n=10). No differences were found in serum resistin levels between obese and control group. Fenofibrate treatment decreased serum triglyceride concentrations, while both blood glucose and glycated hemoglobin increased after three months of fenofibrate administration. Serum adiponectin or resistin concentrations were not significantly affected by fenofibrate treatment. All parameters of insulin sensitivity as measured by hyperinsulinemic-isoglycemic clamp were significantly lower in an obese diabetic group compared to the control group before treatment and were not affected by fenofibrate administration. We conclude that administration of PPAR-α agonist fenofibrate for three months did not significantly affect insulin sensitivity or resistin and adiponectin concentrations in obese subjects with type 2 diabetes mellitus. The lack of insulin-sensitizing effects of fenofibrate in humans relative to rodents could be due to a generally lower PPAR-α expression in human liver and muscle.

Key words
Fenofibrate • Insulin sensitivity • Adiponectin • Resistin • Diabetes

Introduction

Peroxisome proliferators-activated receptors (PPARs) belong to the nuclear receptor superfamily of ligand-activated transcription factors (Torra *et al.* 2001). PPARs regulate lipid and glucose metabolism, cell proliferation and differentiation, inflammation and numerous other processes. To date, three different

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subtypes of PPARs have been identified: PPAR-α, PPAR-γ and PPAR-δ/β (Kersten *et al.* 2000). PPAR-γ is expressed most abundantly in adipose tissue and is considered an essential regulator of adipocyte differentiation and its endocrine function (Saltiel and Olefsky 1996, Olefsky 2000). In addition to its action in adipose tissue numerous direct effects have been documented in the muscle, liver and other tissues (Gavrilova *et al.* 2003, Matsusue *et al.* 2003, Norris *et al.* 2003). PPAR-γ agonists – thiazolidinediones are used as insulin-senziting drugs in the treatment of type 2 diabetes mellitus. PPAR-β/δ occurs practically in all tissues and plays a role in the organ development, embryo implantation, myelinization of corpus callosum, epidermal cell proliferation and lipid metabolism (Peters *et al.* 2000). PPAR-α is expressed in brown adipose tissue, liver, kidney, heart, muscle tissue and gastrointestinal tract and has been recognized as a master regulator of lipid metabolism (Lee *et al.* 1995, Fruchart *et al.* 2001, Gilde *et al.* 2003). Its activation increases transcription of genes involved in transport and oxidation of free fatty acids. Exogenous ligands of PPAR-α – fibrates – have been used for many years as effective hypolipidemic drugs with major triglyceride and free fatty acid lowering effects (Fruchart *et al.* 2001).

A number of recent studies underlined the close interrelationships between obesity/insulin resistance, type 2 diabetes, dyslipidemia with increased triglyceride and free fatty acid levels and decreased HDL cholesterol levels and several other pathological states commonly referred to as metabolic or Reaven´s syndrome (Reaven 1988, 1992). Furthemore, ectopic lipid storage in non-adipose tissues together with endocrine dysfunction of adipose tissue have been demonstrated as major causes of insulin resistance at the postreceptor level of insulin signaling cascade (Ravussin and Smith 2002, Shulman 2000). Another possible etiopathogenetic mechanism interconnecting different pathologies within metabolic syndrome represents disturbed endocrine secretion of adipose tissue (Haluzík *et al.* 2004, Havel 2002, Housa *et al.* 2006, Housová *et al.* 2005).

Several experimental studies including the results of our group demonstrated that activation of PPAR-α decreased ectopic lipid content in the liver and muscle tissues with subsequent improvement in insulin sensitivity in obese mice (Guerre-Millo *et al.* 2000), obese rats (Lee *et al.* 2002), lipoatrophic mice (Chou *et al.* 2002) and mice with insulin resistance induced by muscle overexpression of dominant negative form of IGF-1 receptor (MKR mice) (Kim *et al.* 2003). Furthermore, fenofibrate treatment of MKR mice not only increased their insulin sensitivity but also improved their insulin secretion (Kim *et al.* 2003).

The results of experimental studies focused on the influence of PPAR-α agonist on insulin sensitivity contrast with controversial findings of clinical studies that failed to provide convincing evidence on the consistent effects of PPAR-α activation on insulin sensitivity (Haluzík and Haluzík 2006). It has to be mentioned that most of these studies did not measure changes of insulin sensitivity by the glucose clamp method and some of them utilized less potent fibrates relative to those currently used in clinical practice. Here we tested the hypothesis that treatment with a potent PPAR-α agonist fenofibrate could improve insulin sensitivity in obese women with type 2 diabetes and we explored the possible role of the changes of endocrine function of adipose tissue in this process.

Methods

Studied subjects

Ten obese females with type 2 diabetes mellitus and serum triglyceride concentrations above 2.0 mmol/l and 10 age-matched healthy normal-weight control women were included in the study. Their body weight remained stable for at least three months before the beginning of the study. The patients were treated with diet, metformin alone or combination of metformin and glimepiride. The diabetic medication remained unchanged three months before the start throughout the entire study. None of the studied subjects suffered from any acute infection. Written informed consent was provided by all participants before being enrolled in the study**.** The study was approved by the Human Ethical Review Committee, First Faculty of Medicine and General University Hospital, Prague, Czech Republic.

Study protocol

Measurements of clinical and hormonal parameters in type 2 diabetes patients were performed at baseline and after 3 months of treatment with PPAR-α agonist – fenofibrate (200 mg, Lipanthyl 267M). Control subjects were examined only once and received no treatment.

Anthropometric examination and blood sampling

All subjects were measured and weighed, the

body mass index was calculated and blood samples were withdrawn after overnight fasting. Serum was obtained by centrifugation and stored in aliquots at –70 °C until further analysis.

Hormonal and biochemical assays

Biochemical parameters were measured by standard laboratory methods in the Department of Biochemistry of the General University Hospital. Serum insulin concentrations were measured by commercial RIA kit (Cis Bio Internatinal, France). Sensitivity was 2.0 μIU/ml, and the intra- and interassay variability were 4.2 % and 8.8 %, respectively. Serum adiponectin concentrations were measured by commercial RIA kit (Linco Research, St. Charles, Missouri, USA). Sensitivity was 1.0 ng/ml, and the intra- and interassay variability were 1.78 % and 9.25 %, respectively. Serum resistin concentrations were measured by commercial ELISA kit (BioVendor, Czech Republic). Sensitivity was 0.2 ng/ml, and the intra- and interassay variability were 3.1 % and 6.5 %, respectively.

Hyperinsulinemic-isoglycemic clamp

Hyperinzulinemic-isoglycemic clamp is based on the principle established by DeFronzo *et al.* (1979). Insulin efficiency was evaluated as the amount of glucose necessary for maintaining the desired glucose levels under the conditions of constant insulin infusion calculated per unit of body weight or body surface. In case of the isoglycemic clamp the desired glucose level equals fasting blood glucose level.

At the beginning of the study, two cannulas were inserted into forearm veins on both arms. One of the cannulas was used to infuse insulin solution (20 IU HM-R insulin in 20 ml 0.9 % saline solution, infusion rate: 1 mIU/kg/min for patients with BMI <30 kg/m^2, 40 mIU/m^2/min for patients with BMI >30 kg/m^2) and glucose solution (20 % glucose solution) + 20 ml 7.5 % KCl in 500 ml 0.9 % sodium chloride solution. Glucose infusion rate was modified according to changes of blood glucose concentration. The second cannula in the contralateral forearm was used for blood sampling for blood glucose in 5-min intervals and insulin measurements at baseline and steady-state period. Blood glucose concentration was measured by a glucometer (Super Glucocard II, Arkray, Japan). Glucose clamp was finished after 3 h when the "steady-state" i.e. period of stable blood glucose concentration was close or equal to the desired value for at least 30 min.

Table 1. Anthropometric, biochemical and hormonal parameters and measures of insulin sensitivity measured by hyperinsulinemic-isoglycemic clamp of control group of healthy women and obese women with type 2 diabetes mellitus before (Obese 1) and after three months of treatment with PPAR-α agonist – fenofibrate (Obese 2).

	Control group	**Obese 1**	**Obese 2**
BMI (kg/m^2)	23.90±0.75	36.89±2.89*	36.78±2.76*
Insulin (μIU/ml)	24.7±3.9	43.36±8.6*	49.54±6.7*
Cholesterol (mmol/l)	5.38±0.21	5.05±0.29	4.84±0.31
HDL-cholesterol (mmol/l)	1.82±0.13	1.07±0.08*	1.14±0.05*
LDL-cholesterol (mmol/l)	3.03±0.14	2.71±0.28	2.75±0.20
Triacylglycerol (mmol/l)	1.20±0.12	2.85±0.44*	2.10±0.28*°
Atherogenic index	2.07±0.20	3.89±0.39*	3.24±0.18*
Blood glucose (mmol/l)	5.00±0.25	8.31±0.75*	9.28±0.90*°
Glycated hemoglobin (%)	3.92±0.11	5.64±0.60*	6.01±0.60*°
M (mg.kg^{-1}.min^{-1})	7.10±0.50	3.38±0.35*	3.65±0.27*
M_{korig} (mg.kg^{-1}.min^{-1})	6.72±0.50	3.73±0.48*	3.63±0.38*
MCR_{glc} (ml.kg^{-1}.min^{-1})	8.00±0.78	2.64±0.39*	2.43±0.36*
M/I (mg.kg^{-1}.min^{-1} per mU.ml^{-1})	0.0590±0.0078	0.0293±0.0045*	0.0215±0.0024*
MCR_{glc}/I (ml.kg^{-1}. min^{-1} per mU.ml^{-1})	0.0705±0.0107	0.0238±0.0238*	0.0235±0.0091*

Values are means ± S.E.M. Statistical significance is from one-way ANOVA and Paired t-test respectively. * $p<0.05$ vs. control group, ° $p<0.05$ obese group 1 vs. obese group 2. M – glucose disposal rate, M_{korig} – glucose disposal rate corrected for urine glucose loss, MCR_{glc} – metabolic clearance rate of glucose, M/I, MCR_{glc}/I – insulin sensitivity index.

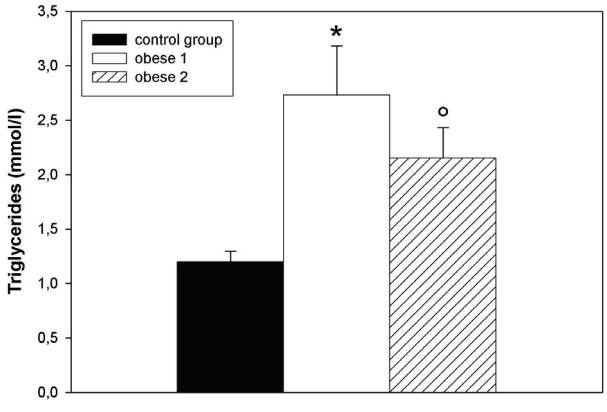

Fig. 1. Serum triglyceride concentrations (mmol/l) in control group (black bar), obese group before (open bar) and after three months of fenofibrate treatment (dashed bar). Values are mean ± S.E.M. Statistical significance is from one-way ANOVA: * $p<0.05$ versus control group, ° $p<0.05$ obese group 1 vs. obese group 2.

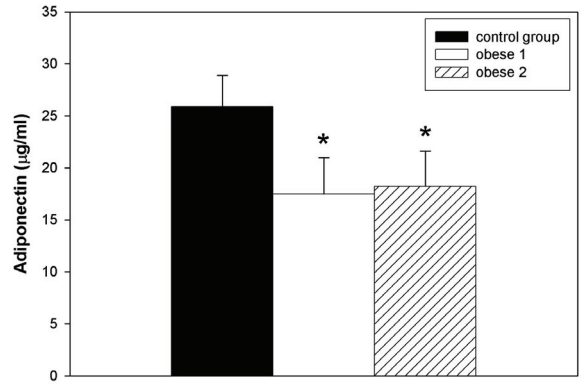

Fig. 2. Serum adiponectin concentrations (µg/l) in control group (black bar), obese group before (open bar) and after three months of fenofibrate treatment (dashed bar). Values are mean ± S.E.M. Statistical significance is from one-way ANOVA: * indicates $p < 0.05$ versus control group.

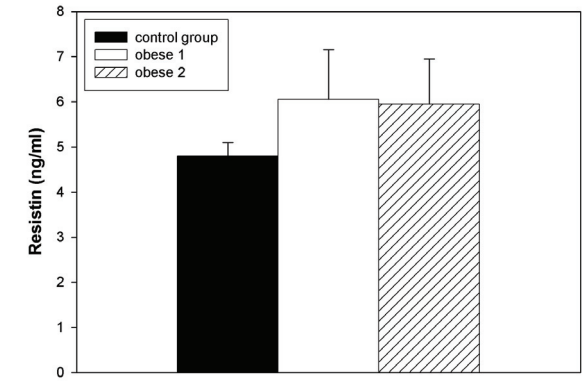

Fig. 3. Serum resistin concentrations (ng/l) in control group (black bar), obese group before (open bar) and after three months of fenofibrate treatment (dashed bar). Values are mean ± S.E.M.

The following parameters were calculated based on clamp results: glucose disposal rate (M, $mg.kg^{-1}.min^{-1}$) was defined as the amount of glucose supplied by the infusion to maintain the desired blood glucose, glucose disposal rate (M_{korig}, $mg.kg^{-1}.min^{-1}$) corrected to urine glucose loss, metabolic clearance rate of glucose (MCR_{glc}, $ml.kg^{-1}.min^{-1}$) was expressed as the ratio of glucose disposal rate to blood glucose concentration and the insulin sensitivity indexes (M/I, $mg.kg^{-1}.min^{-1}$ per $mU.ml^{-1}$, and MCR_{glc}/I $ml.kg^{-1}.min^{-1}$ per $mU.ml^{-1}$) were defined as the ratio of M or MCR_{glc} and the average insulin concentration during the observed period (steady-state), respectively.

Statistical analysis

The statistical analysis was performed on SigmaStat software (Jandel Scientific, USA). The results are expressed as means ± S.E.M.. Data of obese women before and after treatment with fenofibrate were compared by paired t-test. Data of obese women vs. control subjects were compared by One-Way Analysis of Variance followed by Dunnet´s test.

Results

Influence of fenofibrate on anthropometric and biochemical parameters

At baseline, body mass index, serum glucose, triglycerides (Fig. 1), glycated hemoglobin concentrations and atherogenic index in the obese diabetic group were significantly higher (Table 1) while serum HDL cholesterol concentrations were significantly lower than in the control group (Table 1). Three months of treatment with fenofibrate led to significant decrease of serum triglyceride concentrations (Fig. 1), while both blood glucose and glycated hemoglobin significantly increased (Table 1). Other parameters including BMI were not affected by fenofibrate treatment (Table 1).

Influence of fenofibrate on hormonal parameters

Serum adiponectin concentrations in obese women before treatment were significantly lower than in the control group and fenofibrate treatment did not affect this parameter (Fig. 2). No differences between the obese diabetic and the control group were found in serum resistin levels either at baseline or after fenofibrate treatment (Fig. 3).

Influence of fenofibrate on insulin sensitivity

At baseline, all parameters of insulin sensitivity as measured by hyperinsulinemic-isoglycemic clamp were significantly lower in obese diabetic women relative to control group (Table 1). Three months of fenofibrate treatment did not significantly affect any of these parameters (M, M_{korig}, MCR_{glc}, M/I, MCR_{glc}/I). All parameters of insulin sensitivity remained significantly lower in obese women with type 2 diabetes mellitus compared to the control group after three months of treatment with fenofibrate.

Discussion

The aim of our study was to determine whether PPAR-α agonist fenofibrate affects insulin sensitivity in obese women with type 2 diabetes mellitus and whether changes of the endocrine function of adipose tissue mediate metabolic effects of this substance. The results of our study did not reveal any influence of fenofibrate on insulin sensitivity. Surprisingly, the parameters of diabetes compensation – fasting blood glucose and glycated hemoglobin – significantly increased despite clear triglyceride-lowering effect of fenofibrate. The reason for the deteriorating of diabetes compensation in our study is not clear, however, decreased insulin sensitivity after ethophyllinclofibrate treatment has previously been reported in another study (Skrha *et al.* 1994).

The lack of fenofibrate influence on insulin sensitivity in our study is in contrast with most but not all (Šedová *et al.* 2004) of previously published experimental studies. For example, it has been shown that PPAR-α agonist administration improved insulin sensitivity in obese mice (Guerre-Millo *et al.* 2000) or rats (Lee *et al.* 2002), mice with lipoatrophic diabetes (Chou *et al.* 2002) and insulin-resistant mice with muscle-specific overexpression of dominant negative form of IGF-1 receptor (Kim *et al.* 2003). In such studies, PPAR-α activation increased fatty acid oxidation in both muscles and liver with a subsequent decrease of ectopic lipid content in both tissues. As a result, insulin sensitivity was probably improved due to enhanced insulin signaling on the postreceptor level. Furthermore, in our study on mice with muscle-specific overexpression of dominant negative form of IGF-1 receptor insulin secretion was enhanced in addition to improvement of insulin sensitivity (Kim *et al.* 2003).

Despite quite convincing experimental data in favor of insulin-sensitizing effects of PPAR-α activation (Guerre-Millo *et al.* 2000, Chou *et al.* 2002, Kim *et al.* 2003), clinical studies performed to date have failed to unambiguously demonstrate the same effects in humans. Although some studies (Ferrari *et al.* 1977, Murakami *et al.* 1984) showed improvement of glucose tolerance and/or insulin sensitivity, other studies failed to confirm this (Rizos *et al.* 2002, Whitelaw *et al.* 2002) similarly as our current study. Škrha *et al.* (1994) observed even worsening of insulin sensitivity after administration of ethophyllinclofibrate for 12 weeks. The reason for discrepancies between experimental and clinical data could be explained by interspecies differences namely the different level of PPAR-α expression in rodent and human tissues. While in rodents PPAR-α expression especially in the liver is very high, its expression in human muscle and liver is much lower (Loviscach *et al.* 2000). Furthemore, long-term PPAR-α agonist administration in most rodent models of obesity significantly reduces the body fat content (Guerre-Millo *et al.* 2000) which in turn may lead to improvement of insulin sensitivity by an indirect mechanism such as decreased free fatty acid concentrations and/or modulation of endocrine functions of the adipose tissue. Indeed, we and others have demonstrated that PPAR-α activation besides reducing body adiposity increased the expression of adiponectin receptor 1 in adipose tissue which may enhance adiponectin insulin-sensitizing effects despite no change in circulating adiponectin levels (Haluzík *et al.* 2006, Tsuchida *et al.* 2005) Interestingly, in our experimental study, an improvement of insulin sensitivity after fenofibrate treatment was accompanied by paradoxical increase of circulating levels of another adipose tissue-derived hormone resistin that normally decreases insulin sensitivity (Haluzík *et al.* 2006). No such changes occurred in our group of obese diabetic women after fenofibrate treatment. It has to be stressed that despite clear triglyceride- and free fatty acid-lowering effects in humans none of the clinical studies including huge clinical trials focused on the cardiovascular effects of fibrates reported decreased body weight or body fat content after long-term fibrate administration.

Lack of a direct effect of fibrates on adipose tissue in humans was also demonstrated in this study. In obese women with type 2 diabetes no change in body weight or body mass index occurred after the treatment with fibrate. Furthermore, fenofibrate administration had no influence on the circulating levels of adipose tissue-

derived hormones adiponectin and resistin.

It has to be mentioned that our study has several limitations that need to be considered when interpreting the data. Firstly, it was performed on a relatively small number of subjects. Secondly, the changes of insulin sensitivity and other parameters were assessed after three months. This time period of fenofibrate treatment was long enough to decrease circulating triglyceride levels, but may not have been sufficient for the effects on insulin sensitivity. The above mentioned arguments may also hold true for the surprising worsening of diabetes compensation that had occurred in our study. Clearly, more prolonged studies on a greater number of subjects are needed for further clarification of the role of PPAR-α activation in the control of insulin sensitivity in humans.

In conclusion, our study on a limited number of subjects failed to demonstrate any change in insulin sensitivity after 3-month administration of fenofibrate. Furthermore, despite a significant decrease of circulating triglyceride levels no change in endocrine function of adipose tissue as measured by serum adiponectin and resistin concentrations had occurred. Thus, our study underlines the interspecies differences in PPAR-α agonist effects between rodents and humans and indicates that in contrast to rodents no direct effects of fibrates on adipose tissue are present in humans.

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