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Treatment of insulin resistance in diabetes mellitus

Harold E. Lebovitz*, Mary Ann Banerji

Department of Medicine, State University of New York Health Science Center, 450 Clarkson Avenue, Brooklyn, NY 11203, USA

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Abstract

Insulin resistance is a condition in which the glycemic response to insulin is less than normal. The change in insulin sensitivity leads to several sets of responses. One set effects the beta cell and leads to its accelerated destruction and the development of diabetes mellitus. The other set generates a series of nontraditional cardiovascular risk factors that result in accelerated atherosclerosis. Both of these sets of responses may have impacts on other tissues such as the nervous system. Insulin resistance is probably the result of increased visceral adiposity with increased release of free fatty acids and cytokines and a decreased release of adiponectin. Treatment of insulin resistance and its associated abnormalities can be achieved by lifestyle modification which results in weight loss, by drugs that reverse the abnormal adipocyte effects, by drugs that improve insulin sensitivity at the level of the liver and by anti-inflammatory agents that block activation of the nuclear factor kappa B cascade.

Keywords: Insulin; Diabetes mellitus; Obesity

1. Introduction

Insulin resistance in obesity and type 2 diabetes mellitus is associated with a cluster of metabolic abnormalities which is now designated the metabolic syndrome (Lebovitz, 2001a,b). The significance of the metabolic syndrome arises from the observations that this syndrome predicts both the development of type 2 diabetes and future cardiovascular disease (Weyer et al., 1999; Isomaa et al., 2001; Hanley et al., 2002). The major unresolved question is whether the metabolic syndrome is caused by a unique underlying abnormality that is expressed within the genetic background of the individual or whether it is the result of multiple abnormalities that cluster together in a variety of forms. If there is a unique underlying abnormality then the possibility exists that an intervention that ameliorates that abnormality may improve or correct all of its components. If, however, it is caused by multiple abnormalities then treatment must involve management of each individual component. The metabolic syndrome carries a much higher relative risk (RR) for the development of type 2 diabetes (RR ~ 5–6) than that for cardiovascular disease (RR ~ 1.3–1.8)(Stern, 1997). The metabolic syndrome is a heterogeneous entity with individuals expressing different clusters of the components. It is unclear whether the heterogeneity is due to differing pathogeneses or differing individual responses to the same pathogenetic mechanism.

Figs. 1 and 2 depict the likely components of the metabolic syndrome that impact the development of type 2 diabetes as compared to those that impact on the pathogenesis of cardiovascular disease (Lebovitz, 2001a,b; Lebovitz and Banerji, 2001). Normal glucose tolerance converts to impaired glucose tolerance and on to type 2 diabetes as a consequence of decreasing beta cell insulin secretory function (UK Prospective Diabetes Study Group, 1995; Lebovitz, 1999). The components of the metabolic syndrome which might contribute to accelerated loss of beta cell function in individuals with a predisposition to type 2 diabetes are represented in Fig. 1. Insulin resistance causes compensatory hyperinsulinemia in everyone (Kahn et al., 1993). Type 2 diabetes occurs in those individuals whose beta cells are genetically predisposed to abnormal function. When those beta cells are subject to the consequences of hyperfunction, the extra metabolic burden increases their already precarious state and their rate of apoptosis and loss of function increase. The decreasing beta cell function is the cause of postprandial and subsequently fasting hyperglycemia (Weyer et al., 1999). Other potential contributory factors to the decreasing beta cell function are lipotoxicity, glucotoxicity, an inflammation

* Corresponding author. Tel.: +1-718-816-4638; fax: +1-718-447-1558.
E-mail address: hlebovitz@attglobal.net (H.E. Lebovitz).

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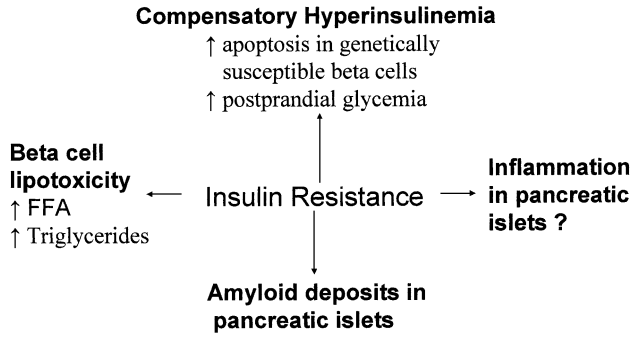

Fig. 1. The potential mechanism by which insulin resistance increases the rate of loss of beta cell function in genetically susceptible individuals.

within the islets and the deposition of amyloid within the islets. Lipotoxicity can arise from increases in free fatty acid (FFA) uptake by the beta cell. Glucose toxicity can be a consequence of elevated postprandial plasma glucose levels. Islet amyloid is a polymerization product of human amylin, which is cosecreted with insulin and is elevated in hyperinsulinemic conditions. Inflammation is a component of the metabolic syndrome and the degree to which it affects the pancreatic islets is unknown, although elevated Plasma C Reactive Protein levels are known to predict future type 2 diabetes (Ridker et al., 2003).

Fig. 2 shows the major classes of cardiovascular risk factors that are components of the metabolic syndrome. While all of these components predict cardiovascular risk, the risk attributed to the metabolic syndrome is said to exceed the sum of the components (Isomaa et al., 2001). These individual risk factors are currently treated individually, i.e., lipid lowering agents, antiplatelet agents, antihypertensive agents and if hyperglycemia is present, antihyperglycemic agents (Gaede et al., 2003).

If the metabolic syndrome were the result of a common abnormality, then a rational approach to its management would be to identify that common pathway and to treat its underlying abnormalities. Insulin resistance would seem to be the appropriate underlying pathway that leads to the metabolic syndrome. Treatment of insulin resistance does appear to improve many of the components of the syndrome. An even more fundamental question to explore is what causes the insulin resistance.

Fig. 3 outlines a hypothesis which can fit with much of the available data. Insulin signaling within the cell is mediated by two functional cascades: one which acts through the phosphoinositol-3 kinase (PI-3 kinase) pathway and one which acts through the mitogen-activated protein kinase (MAP kinase) pathway (Virkamaki et al., 1999). The PI-3 kinase pathway is the one that mediates insulin's effects on intermediary metabolism and nitric oxide (NO) generation (Flier and Mantzoros, 2001). The MAP kinase pathway mediates cell growth and mitoses. Clinical insulin resistance as seen in obesity and type 2 diabetes involves only the PI-3 kinase pathway (Dib et al., 1998). Thus, some actions of insulin are resistant and others are not. Considerable data suggest that the insulin resistance associated with the metabolic syndrome and type 2 diabetes results from an inhibition of the tyrosine phosphorylation of insulin receptor substrates (IRS) and the PI-3 kinase subunits (Dresner et al., 1999). The inhibition occurs because serine and threonine residues on those molecules have been phosphorylated by serine phosphorylases that have been activated by products of fatty acid metabolism, cytokines and the inflammatory cascade [Nuclear Factor Kappa B ($NF_{\kappa}B$)]. These products are in large part the result of changes in adipocyte metabolism. Increased food intake and decreased physical conditioning result in an increase in body fat in general and visceral adipose tissue in particular. The increased release of some visceral adipose tissue products and the decrease in the adipose tissue hormone adiponectin result in increased hepatic fat and a cascade of metabolic effects that result in the metabolic syndrome (Lebovitz, 2001a,b, 2003).

These hypotheses would predict that insulin resistance and the metabolic syndrome could be treated by lifestyle modification which decreases visceral obesity and increases physical conditioning, by drugs that reverse the abnormal adipocyte effects, by drugs that improve insulin sensitivity at the level of the liver and by antiinflammatory agents that block activation of the Nuclear Factor Kappa B ($NF_{\kappa}B$) cascade (Fig. 4).

2. Treatment of insulin resistance by lifestyle modification

Studies in obese insulin-resistant individuals show that weight loss improves insulin sensitivity as well as many of the other components of the metabolic syndrome. While there is not universal agreement, many studies indicate that an increased intraabdominal (visceral) adipose tissue depot is the major determinant of insulin resistance and that weight loss improves insulin sensitivity by reducing the visceral adipose tissue depot. Visceral adipose tissue is more sensitive to lipolytic hormones and less sensitive to insulin effects than subcutaneous adipose tissue (Lebovitz, 2003). A critical review of 23 separate studies that evaluated the effects of dietary or pharmacologic treatments on weight

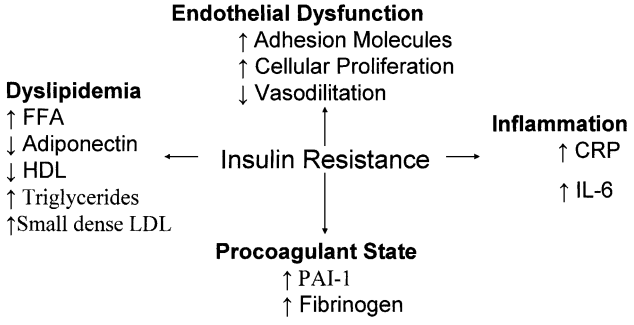

Fig. 2. The associated metabolic abnormalities that cluster with insulin resistance and comprise the metabolic syndrome.

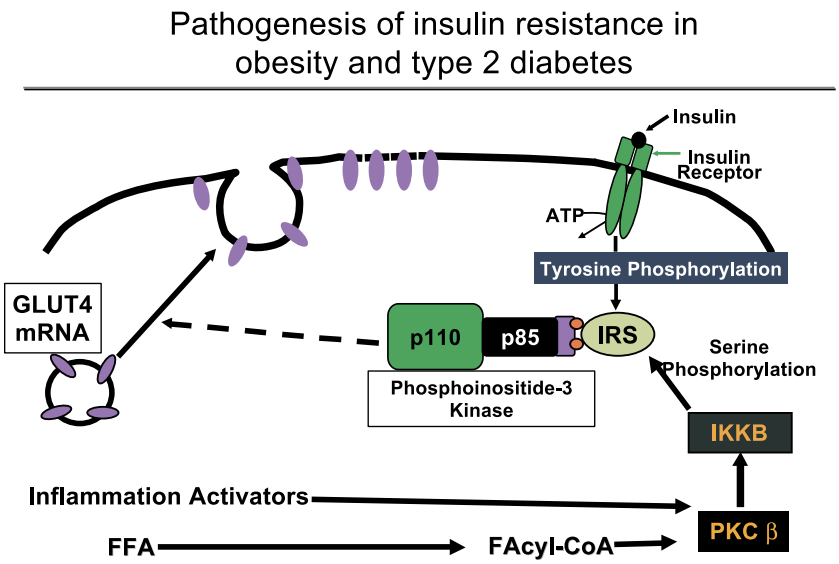

Fig. 3. A proposed mechanism for the pathogenesis of insulin resistance in obesity and type 2 diabetes. See text for description.

loss reported a preferential loss of visceral fat over total fat regardless of the intervention (Smith and Zachweija, 1999). Relative loss of visceral fat was most in those individuals who had a greater visceral fat mass either through a greater increase in body weight or a greater propensity to store calories as visceral fat.

Table 1 presents illustrative data from several recent weight loss studies. In all the studies, the loss in subcutaneous adipose tissue paralleled the loss in total adipose tissue. That was so despite the fact that in all of the studies except Pare et al. (2001), the subcutaneous and visceral adipose tissue masses were determined by the area in a single CAT scan through the lumbar region. Pare et al. (2001) used two CAT scans, one performed at lumbar vertebrae 2 to lumbar vertebrae 3 and one at lumbar vertebrae 4 to lumbar vertebrae 5 and calculated the corresponding cylinder volume. The percent reduction in visceral adipose tissue exceeded that in total and subcutaneous adipose tissue in most but not all studies. Each of the studies had a different design and identified different issues. Shadid and Jensen (2003) noted a decrease in fat cell lipid content in the abdominal but not the femoral subcutaneous adipose tissue depot. The 62% greater reduction in visceral adipose tissue was associated with significant improvements in fasting plasma glucose, insulin and triglycerides. Lynch et al. (2001) combined a hypocaloric diet with increased physical activity. An increase in physical

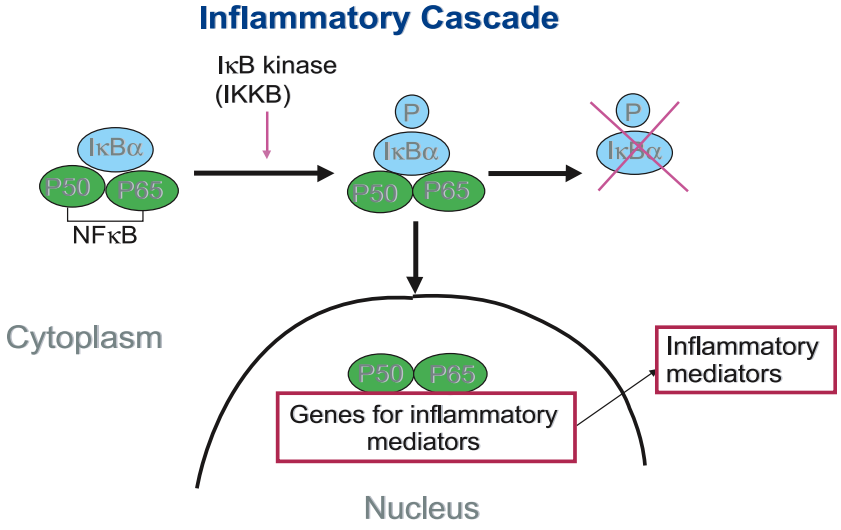

Fig. 4. The Nuclear Factor Kappa B ($NF_\kappa B$) inflammatory cascade. $NF_\kappa B$ is stored in the cytoplasm complexed with Inhibitory Kappa B Alpha (IκBα). An inflammatory agent activates the enzyme Inhibitory Kappa B Kinase (IκB kinase) which phosphorylates IκBα. The phosphorylated subunit separates from the complex and is metabolized. The free $NF_\kappa B$ migrates in to the nucleus and activates genes with $NF_\kappa B$ recognition sites. Those genes transcribe the mRNA for the inflammatory mediators.

Table 1
Recent dietary and exercise interventions in the treatment of obesity

Parameter	Goodpaster		Shadid	Lynch	Pare	Pontiroli	Weinsier		Tchernof
	Women	Men					White	Black	
Men (*n*)		15	10		45	27			
Women (n)									
Premenopausal	17		9			58	23	23	
Postmenopausal				40		58			25
Weight (kg)	92.5	109.0	97.5	81.0	94.3	BMI 44.9	78.2	79.1	93.0
Study duration (weeks)	18	18	20	26	52	52	22 ± 7	25 ± 14	60 ± 11
Percent change									
Weight	− 13.2	− 16.1	− 12.0	− 8.0	− 4.3	− 17.8	− 13.1	− 12.6	− 15.6
Total fat	− 24.3	− 35.5	− 26.0	− 17.0	− 9.5		− 34.6	− 32.4	− 25
Visceral A.T.	− 29.9	− 46.7	− 39.4	− 16.7	− 17.4	− 49.2	− 39.2	− 41.7	− 36.4
S.C. A.T.	− 25.5	− 34.2	− 24.3	− 17.4	10.7	− 16.8	− 41.0	− 33.1	− 23.7
FBG	− 2.1	− 4.2	− 5.2			− 12.9			
FPI	− 44.1	− 53.5	− 37.5			− 44.0			
Cholesterol	− 7.8	+ 10.0	− 20.9			+ 1.9			+ 5.0
HDL	0	− 8.5	− 2.6			+ 11.4			+ 60.6
TG	− 28.6	− 35.2	− 37.0			− 29.4			− 15.0

The effect of the interventions on percent changes in weight, total body fat, adipose tissue depots and components of the metabolic syndrome are tabulated.

conditioning as estimated by an increase in V_{O2} max resulted in weight loss with marked reduction in visceral fat mass. Weight loss without an increase in physical conditioning resulted in a significantly lesser proportion of visceral fat mass loss as compared to the total and subcutaneous fat mass. Pontiroli et al. (2002) noted that the weight loss from laparoscopic gastric banding reached its maximum after 1 year and was associated with a threefold greater loss of visceral adipose tissue as compared to subcutaneous adipose tissue as well as marked improvement in the measured components of the metabolic syndrome. Goodpaster et al. (1999) found that only the percent reduction in visceral adipose tissue predicted the improvement in insulin sensitivity associated with weight loss in their patients. Black women have been shown in several studies to have relatively less visceral adipose tissue than white women with comparable degrees of obesity (Albu et al., 1997). The significance of this observation is not clear. Weinsier et al. (2001) found the same in their study of weight loss in premenopausal women. Despite 40% less visceral fat at baseline, their obese black women lost the same percentage of visceral fat as did the white women during comparable weight loss.

The increased turnover of visceral adipose tissue during weight loss likely accounts for the dramatic improvement in insulin resistance which occurs in obese individuals who have as little as a 5–10% decrease in body weight. The visceral adipose tissue depot appears to be the source of the flux of adipose tissue products that are released and subsequently modulate insulin action (Lebovitz, 2003). Therefore, while the volume of intraabdominal adipose tissue is correlated with insulin sensitivity, there are instances where the volume of visceral fat is normal or decreased, yet the flux of visceral adipose tissue products may be abnormal and cause insulin resistance. This is seen in various lipoatrophic states or in animals or humans with abnormalities of adipose tissue formation (Gurnell et al., 2003).

Weight loss in obese insulin-resistant individuals also decreases some of the nontraditional cardiovascular risk factors which are part of the metabolic syndrome. Plasminogen activator inhibitor 1 (PAI-1) is produced in excessive quantities by adipose tissue and endothelial cells in insulin-resistant individuals and decreases fibrinolytic activity (Janand-Delenne et al., 1998). Weight loss decreases the elevated plasma PAI-1 levels (Kockx et al., 1999; Mavri et al., 1999, 2001). The decrease is consistently correlated with the decrease in total body fat and occasionally appears to be related to decreases in the visceral adipose tissue depot. Similarly, plasma C-reactive protein which is a marker of the inflammatory component of the metabolic syndrome is also reduced by weight loss, and this effect correlates with both the reduction in total body fat and the reduction in visceral adipose tissue (Tchernof et al., 2002).

The composite data on weight loss can be summarized as follows:

1. Weight loss improves insulin sensitivity.
2. Weight loss decreases triglycerides and in some studies increases high-density lipoprotein (HDL) cholesterol.
3. Weight loss decreases the procoagulant state.
4. Weight loss reduces the inflammatory state.

As a consequence of its improvement in insulin action, weight loss decreases hyperinsulinemia and should lessen the factors which contribute to the accelerated loss of beta cell function depicted in Fig. 1. Therefore, weight loss of between 5% and 10% of baseline body weight should decrease the development of new cases of type 2 diabetes in obese insulin-resistant individuals with Impaired Glucose

Tolerance. Two recent lifestyle intervention studies have validated that hypothesis. A large randomized Finnish study comparing an intensive dietary and exercise program to an ordinary dietary program in obese subjects with Impaired Glucose Tolerance showed that a 5% reduction in body weight decreased new cases of type 2 diabetes by 58% over a 3-year period (Tuomilehto et al., 2002). A similar though much larger US study which recruited patients of African, Hispanic, Native American, and Asian origins as well as Caucasians showed that a mean weight loss of 7% in obese Impaired Glucose Tolerant individuals reduced new cases of diabetes from 11.0% per year to 4.8% per year over a 3-year period (Knowler et al., 2002). Although the data on changes in insulin sensitivity in those studies are not yet available, it appears that reduction in insulin resistance was the major factor responsible for the prevention of the development of diabetes.

3. Treatment of insulin resistance with peroxisome proliferator-activated receptor γ (PPARγ) agonists

3.1. Mechanism of increasing insulin sensitivity

Peroxisome proliferator-activated receptor γ (PPARγ) agonists are molecules that bind to a nuclear transcription factor which is a heterodiamer containing binding sites for both it and retinoid molecules. The PPARγ–retinoid bound complex searches for and attaches to genes with sites which recognize that unique complex. After binding to the specific DNA response regions, the gene heterodiamer unit recruits the appropriate coactivator elements and transcription is activated (Willson et al., 2000, 2001; Lebovitz and Banerji, 2001). The genes activated by PPARγ agonists are ones that are involved in regulating insulin action, adipose cell differentiation and some aspects of lipid metabolism. The natural ligands for the PPARγ receptor remain unclear, although several polyunsaturated fatty acids and eicosanoids have been shown to activate the receptor.

While several structural classes of compounds have been shown to have PPARγ agonist activity, the only PPARγ agonists for which significant human data exist are the thiazolidinediones. Consequently, this section will focus primarily on results reported with pioglitazone, rosiglitazone and troglitazone. Troglitazone is unique in that its administration was associated with a rare but fatal idiosyncratic hepatotoxicity (Lebovitz, 2002b). Thus, it was removed from the market and clinical use in March 2000. Extensive clinical studies and postmarketing surveillance have shown that neither pioglitazone nor rosiglitazone has this hepatotoxic effect (Lebovitz et al., 2002). While it is possible that there may be subtle differences between the effects of pioglitazone and rosiglitazone, there are no comparative controlled blinded studies to validate any significant differences.

The mechanism by which PPARγ agonists improve insulin resistance is most likely secondary to their effects on adipose tissue rather than a direct effect on either muscle or liver (Willson et al., 2001; Lebovitz, 2002a; Gurnell et al., 2003). The highest concentrations of PPARγ receptors are found in adipocytes which contain predominately the $PPAR\gamma_2$ subtype. PPARγ receptor activation plays a major role in adipocyte differentiation. This is particularly true for subcutaneous adipocytes and not visceral adipocytes. Studies in humans with both pioglitazone and rosiglitazone show that administration of these agents to adults increases subcutaneous adipose tissue approximately 3.5% and has little or no effect on visceral adipose tissue (Lebovitz and Banerji, 2001; Lebovitz, 2002a). Thiazolidinedione treatment decreases plasma free fatty acids from 25% to 35% (Lebovitz et al., 2001), lowers circulating TNFα and other cytokines and raises plasma adiponectin levels (Yang et al., 2002; Yu et al., 2002). It is unclear to what extent the thiazolidinedione improvement in insulin sensitivity is due to an effect on product release from visceral fat vs. an increase in fat product removal by the new adipocytes created in the subcutaneous fat. Improvement in insulin sensitivity in insulin-resistant subjects has been assessed by euglycemic–hyperinsulinemic clamps, frequently sampled intravenous glucose tolerance and the HOMA-IR model. Thiazolidinediones increase insulin sensitivity in insulin-resistant subjects between 25% and 68% depending on the particular study and technique used (Chu et al., 2002; Mayerson et al., 2002; Miyazaki et al., 2001; Pavo et al., 2003).

3.2. Effects on dyslipidemia

Treatment of insulin-resistant humans with thiazolidinediones dramatically improves the dyslipidemia which is characteristic of insulin resistance. Low-density lipoprotein (LDL) particles which are predominately small and dense in insulin-resistant individuals are converted to large and buoyant ones with rosiglitazone or pioglitazone treatment (Freed et al., 2002; Winkler et al., 2003). Plasma HDL cholesterol levels are increased by 10–20% during treatment with pioglitazone or rosiglitazone, and the HDL cholesterol increase is predominately in the large HDL_2 particles (Lebovitz, 2002a; Freed et al., 2002). The plasma triglyceride levels are modestly reduced by thiazolidinediones if they are elevated (>200 mg/dl). Some authors have suggested that pioglitazone may have a greater effect in lowering plasma triglycerides than rosiglitazone; however, a blinded controlled comparative study is needed to determine if this is so. Because the LDL particle is increased in size and buoyancy by thiazolidinediones, it is obvious that the plasma LDL cholesterol concentration also rises a small quantity (~ 7–10%). The dyslipidemia of insulin resistance is associated with increased cardiovascular morbidity and mortality (Robins et al., 2003). Improvement in that dyslipidemia by gemfibrozil in the Veterans Affairs HDL

Intervention Trial reduced composite cardiovascular endpoints by 32% (Rubins et al., 2002).

3.3. Effects on endothelium

Thiazolidinedione treatment improves the endothelial dysfunction which occurs with insulin resistance (Parulkar et al., 2001; Caballero et al., 2003). Insulin acts on endothelial cells to activate nitric oxide synthase which catalyzes the production of nitric oxide from arginine. This effect of insulin is mediated through the PI-3 kinase cascade and is impaired in insulin-resistant states (Calnek et al., 2003). This leads to endothelial dysfunction which is associated with increased vascular resistance and decreased vasodilation, increased production of adhesion molecules which bind platelets and leukocytes, increased proliferation of smooth muscle cells and fibroblasts and increased permeability. Treatment of type 2 diabetic patients or nondiabetic subjects with insulin resistance with thiazolidinediones improves endothelial dysfunction through nonglycemic mechanisms (Paradisi et al., 2003). Flow-mediated vasodilatation is increased. Mean 24-h systolic and diastolic blood pressure is decreased 4–5 mm Hg in both type 2 diabetic patients and in nondiabetic hypertensive subjects (Raji et al., 2003; Fullert et al., 2002). The production of adhesion molecules, Vascular Cell Adhesion Molecule 1 (VCAM-1) and Intercellular Adhesion Molecule 1 (ICAM-1), are decreased (Pasceri et al., 2000). Vascular smooth muscle cell proliferation is inhibited (Hsueh et al., 2001; Law et al., 2000). Neointimal tissue proliferation after coronary stent implantation in type 2 diabetic patients is reduced 50–70% by thiazolidinedione treatment (Takagi et al., 2003). Several studies have shown that thiazolidinediones increase vascular endothelial cell growth factor (VEGF) expression which is probably secondary to their effects in blocking VEGF's downstream biological actions (Murata et al., 2001; Emoto et al., 2001).

3.4. Effects on inflammation

An inflammatory response is part of the metabolic syndrome and it is modulated by PPARγ agonists (Pasceri et al., 2000). Elevation of plasma C-reactive protein predicts the future development of type 2 diabetes as well as cardiovascular disease (Festa et al., 2003). Treatment with either pioglitazone or rosiglitazone reduces the mean plasma C-reactive protein levels in type 2 diabetic patients or nondiabetics with insulin resistance by 25–30% (Haffner et al., 2002; Sidhu et al., 2003; Yatagai et al., 2004). Other markers of inflammation, such as white blood cell counts and metalloproteinase 9 which are elevated in insulin-resistant states, are also reduced by thiazolidinedione treatment (Haffner et al., 2002). A recent study suggests that C-reactive protein plays a direct role in promoting atherogenesis by activating inflammatory ($NF_{\kappa}B$) and proliferative (MAP kinase) pathways in vascular smooth muscle cells (Hattori et al., 2003).

3.5. Effects on procoagulant state

Insulin resistance is associated with an increase in plasma fibrinogen (acute phase reactant) and an elevation in plasminogen activator inhibitor 1 (PAI-1) (Lebovitz, 2001a,b). PAI-1 functions to prevent excessive activation of plasminogen to plasmin by tissue plasminogen activator (tPA) (Kohler and Grant, 2000). Elevated levels of PAI-1 cause impaired fibrinolysis and are known risk factors for cardiovascular disease. The excessive production of PAI-1 in insulin-resistant subjects comes from the increased adipose tissue mass and the dysfunctional endothelial cells. Treatment of insulin resistance with thiazolidinediones reduces plasma PAI-1 activity approximately 25% and allows for more normal fibrinolytic activity (Kruszynska et al., 2000; Harte et al., 2003).

3.6. Effect on glycemic control in patients with type 2 diabetes

Approximately 80–85% of patients with phenotypic type 2 diabetes have insulin resistance as a major contributory factor in the development of their disease (Lebovitz, 2001a,b). The insulin resistance usually precedes the glucose abnormalities and facilitates the progression of impaired fasting glucose or impaired glucose tolerance to type 2 diabetes by accelerating beta cell functional deterioration (Weyer et al., 1999). The initial response to insulin resistance is compensatory hyperinsulinemia (Kahn et al., 1993). As long as the beta cells can compensate for the insulin resistance with sufficient insulin secretion to overcome the resistance, glucose metabolism will remain normal. As beta cell function decreases, as is characteristic of individuals genetically predisposed to type 2 diabetes, glucose intolerance ensues. Thus, hyperglycemia is the consequence of an imbalance between insulin requirements and insulin availability.

Treatment of type 2 diabetic patients with thiazolidinediones improves glycemic control by improving the effectiveness of circulating insulin (Lebovitz, 2002a). If therapy is instituted when beta cell function is approximately 50% of normal (mean HbA1c 8.5–9.0% on diet), monotherapy will improve glycemic control such that the mean decrease in HbA1c is 1.5% with about 30% of patients attaining a HbA1c < 7.0% (Lebovitz et al., 2001). If endogeneous beta cell function is more severely impaired, the thiazolidinedione will need to be combined with other therapies that increase insulin availability (insulin secretogogues or exogenous insulin) or provide additional improvement in insulin resistance (metformin).

The magnitude of improvement of glycemic control is a function of the degree of improvement of insulin sensitivity and the available circulating insulin. Nonglycemic effects of

thiazolidinediones are dissociable from their glycemic effects (Satoh et al., 2003; Yatagai et al., 2004).

3.7. Effects in preserving beta cell function

Decreasing beta cell function in individuals with the predisposition to develop type 2 diabetes appears to be due to a combination of factors which include genetic programming, the metabolic and increased work load imposed by insulin resistance and lipotoxicity and glucotoxicity. The impact of insulin resistance can be decreased by treatment of prediabetic individuals with thiazolidinediones. Two studies, the TRIPOD study and the DPP, have shown that administering troglitazone to individuals with impaired glucose tolerance reduces the development of new cases of diabetes. The TRIPOD study showed a 56% decrease in new cases of type 2 diabetes over 30 months in women who had had gestational diabetes which reverted to normal or impaired glucose tolerance after delivery (Buchanan et al., 2002). The placebo-treated group developed diabetes at a rate of 12.1% per year as compared to 5.4% per year in the troglitazone-treated group. Those features which predicted the prevention of type 2 diabetes were the degree of improvement in insulin action by the thiazolidinedione, and the magnitude of beta cell function that had persisted at the time that the intervention was started. Longitudinal measurements of beta cell function showed that the placebo-treated group lost 39% over the duration of the study, while the Troglitazone-treated group lost only 3%. Clinical studies with rosiglitazone such as the DREAM study are currently underway to confirm that beta cell preservation is a class effect of thiazolidinediones.

3.8. Effects on weight gain and fluid retention

Thiazolidinediones as a class have two major side effects, increased adiposity and fluid retention (Lebovitz, 2002b). As noted earlier, PPARγ agonists cause the differentiation of stem cells into adipocytes. This occurs in subcutaneous adipose tissue but not in visceral adipose tissue. The increase in subcutaneous adipose tissue and weight gain is dose related. The average weight gain on the maximal monotherapy dose is 3.5–4.0 kg (Mudaliar et al., 2003; Nesto et al., 2003).

Fluid retention occurs and is manifested as a small decrease in hemoglobin and hematocrit in most patients and mild to moderate peripheral edema in 4–5% of patients taking thiazolidinediones as monotherapy (Lebovitz and Banerji, 2001). When thiazolidinediones are combined with sulfonylureas, peripheral edema occurs in 6% or 7% of the patients. This increases to approximately 15% when the drugs are combined with insulin. The mechanism responsible for the fluid retention has not been precisely defined but appears to involve a renal mechanism. Usual therapies for fluid retention are only modestly effective in thiazolidinedione-induced fluid retention, and discontinuation of the drugs is frequently necessary when the fluid retention is severe (Tang et al., 2003).

Several reports have associated the precipitation of congestive heart failure in type 2 diabetic patients with the administration of thiazolidinediones (Nesto et al., 2003; Tang et al., 2003). This complication is very uncommon, occurs in older individuals with preexisting cardiovascular or renal disease, and is usually seen with the highest doses of thiazolidinediones and in combination with insulin treatment. The most likely explanation is that the thiazolidinedione-induced increase in plasma volume in individuals with asymptomatic or compensated heart failure precipitates symptomatic failure. If thiazolidinediones are administered to type 2 diabetic patients who are predisposed to congestive heart failure, the drugs should be initiated at the lowest dose and titrated up slowly. The patients should be monitored carefully for signs or symptoms of heart failure.

4. Treatment of insulin resistance with metformin

Metformin has been used for the treatment of type 2 diabetes for more than 40 years. It is highly effective in improving glycemic control and in contrast to other therapies for type 2 diabetes, it is associated with a small weight loss (1–2 kg) (UK Prospective Diabetes Study Group, 1998). Its mechanism of action is still debated, but it is clear that its action is extrapancreatic. Treatment of type 2 diabetes with metformin causes a decrease in both plasma glucose and insulin, and therefore, by definition it is an insulin sensitizer (Inzucchi et al., 1998; Yu et al., 1999). Metformin was the only treatment used in the United Kingdom Prospective Diabetes Program (UK Prospective Diabetes Study Group, 1998), which caused a statistically significant decrease in myocardial infarctions and diabetes-related deaths. The improvement in glycemia in the overweight type 2 diabetic patients in the UKPDS was no greater with metformin than with the other treatments and the cardioprotective effects of metformin must be attributed to some nonglycemic effect of metformin.

Metformin improves insulin sensitivity and partially ameliorates some of the components of the metabolic syndrome (Chu et al., 2002; Hallsten et al., 2002; Pavo et al., 2003). The mechanisms and spectrum of metformin action are somewhat different from the thiazolidinediones (Pavo et al., 2003; Chu et al., 2002; Hallsten et al., 2002; Virtanen et al., 2003). The similarities and differences are summarized in Table 2. Metformin and thiazolidinediones improve glycemia in type 2 diabetics equally (Lebovitz, 2001b). Metformin improves total body insulin-mediated glucose uptake in type 2 diabetic patients only to the extent that it improves glycemic control and promotes weight loss. That is, it has no direct effects on insulin-mediated muscle glucose uptake, and any effects observed are only the result of an improvement in glucose toxicity and weight loss (Hallsten et al., 2002; Yu et al., 1999; Inzucchi et al.,

Table 2
Comparison of the effects of thiazolidinediones and metformin on insulin resistance and the components of the metabolic syndrome

Activity	Metformin	Thiazolidinediones
Glycemic control		
FPG	↓↓	↓↓
HbA1c	↓↓	↓↓
FPI	↓	↓↓
Body weight	↓	↑
Visceral fat	↓	0
Insulin sensitivity		
Peripheral	±	↑↑
Liver	↑↑	↑
Dyslipidemia		
LDL cholesterol	±	↑
LDL particle size	0	↑
HDL cholesterol	±	↑↑
Triglyceride	±	↓
Lp(a)	0	↑
FFA	±	↓↓
Endothelial function		
Vasodilation	↑	↑↑
Blood pressure	0	↓
Adhesion molecules		↓
Muscle proliferation		↓
Procoagulant state		
PAI-1	↓	↓
Fibrinogen		
Inflammation		
C-reactive protein	↓	↓
Mesangial function		
Microalbuminuria	↓	0

0 = no effect, ↓ = decrease, ↓↓ = marked decrease, ↑ = increase, ↑↑ = marked increase.

1998; Pavo et al., 2003). In contrast, thiazolidinediones have major direct effects in improving insulin-mediated muscle glucose uptake. Metformin does have significant direct effects in improving insulin action on the liver. This leads to decreased hepatic glucose production and fasting plasma glucose. As a total, body insulin sensitizer thiazolidinediones are approximately 70% greater than metformin (Yu et al., 1999). The greater decrease in plasma insulin levels with thiazolidinediones than metformin are further evidence of this greater effect. Because the mechanisms of improving insulin action and the primary target organs of metformin and thiazolidinediones are different, the additive effects of these two classes of drugs in insulin-resistant patients that have been demonstrated were to be expected (Fonseca et al., 2000; Einhorn et al., 2000).

Metformin has been shown to cause small decreases in plasma triglycerides and LDL cholesterol in some but not all studies (DeFronzo and Goodman, 1995; Chu et al., 2002; Pavo et al., 2003). Metformin has little or no effect on high-density lipoprotein cholesterol or low-density lipoprotein particle size. In contrast to thiazolidinediones, metformin treatment causes a small decrease in both subcutaneous and visceral adipose tissue.

Metformin treatment improves many of the vascular and inflammatory components of the metabolic syndrome such as insulin-mediated vasodilation, plasma C-reactive protein, and PAI-1, but these improvements are less than those achieved by thiazolidinedione treatment (Charles et al., 1998; Mather et al., 2001; Gin et al., 2003; Hadigan et al., 2001; Chu et al., 2002). Other actions such as nonglycemic-mediated decrease in microalbuminuria, inhibition of vascular smooth muscle cell proliferation, decrease in systolic and diastolic blood pressure, and decreases in adhesion molecules are not ordinarily seen with metformin treatment.

5. Treatment of insulin resistance with antiinflammatory agents

Studies in laboratory animals and preliminary studies in humans have led to a hypothesis that factors which cause insulin resistance in humans with obesity and type 2 diabetes mediate their effects through the Nuclear Factor kappa B ($NF_{\kappa}B$) inflammatory cascade (Tak and Firestone, 2001; Lebovitz, 2003). Infusion of intralipid and heparin to laboratory animals and humans raises plasma free fatty acid (FFA) levels and causes resistance to insulin action. The FFA-induced insulin resistance can be ameliorated by anti-inflammatory agents that block the activation of the intracellular enzyme Inhibitory κB kinase (IκB kinase) (Hundal et al., 2002). Elevated plasma FFAs do not cause insulin resistance in IκB knock out mice (Yuan et al., 2001). This intriguing hypothesis needs to be extensively tested.

6. Conclusions and potential implications for central nervous system disorders

Several recent reports have suggested that insulin resistance, and/or abnormal insulin action may be involved in the development of central nervous system disorders such as Alzheimer's disease. Ischemic strokes, Alzheimer's disease and multiple sclerosis are characterized by abnormal cellular metabolism and activated inflammatory processes. Because peroxisome proliferator-activated receptor (PPAR) agonists might affect such processes, there has been an increasing interest in whether PPAR agonists might be useful therapeutic agents for these disorders.

PPAR isoforms are found throughout the central nervous system. PPARβ (also referred to as PPARδ) receptors are the PPAR isoform most widely expressed throughout the brain (Woods et al., 2003). They are localized within oligodendrocytes and neurons. In vitro studies suggest that both PPARβ and PPARγ agonists increase the number of oligodendrocytes and extend their cell processes (Saluja et al.,

2001; Roth et al., 2003). Preliminary data suggest that PPARβ may regulate brain lipid metabolism through transcriptional control of genes such as acyl-CoA synthase 2 (Basu-Modak et al., 1999). PPARα and PPARγ receptors are also found in the brain but in a more restricted pattern. The frontal cortex, basal ganglia, reticular formation, some cranial nerve nuclei, deep cerebellar nuclei and cerebellar Golgi cells in adult rat brain have been shown to contain significant quantities of all the PPAR isoforms (Moreno et al., 2004). Primary and secondary cultures of astrocytes from neonatal rat brain express the different PPAR isoforms, and differences in expression depend on the brain area from which they are isolated and the age of the animal (Cristiano et al., 2001).

One might therefore anticipate that PPAR agonists with their diverse metabolic effects on insulin resistance, lipid metabolism and inflammation might have an effect on brain function and could have applicability in the treatment of some neurological disturbances. Several experimental animal studies show that PPARα agonists protect against ischemic injury in the brain (Deplanque et al., 2003; Inuoe et al., 2003). A 14-day preventative treatment with fenofibrate (a PPARα agonist) reduced susceptibility to stroke in apolipoprotein E-deficient mice and decreased cerebral infarct size in C57BL/6 wild-type mice. The neuroprotective effect of fenofibrate is absent in PPARα-deficient mice (Inuoe et al., 2003).

Thiazolidinedione drugs have been shown to increase glucose consumption and lactate production by astrocytes during in vitro incubation (Dello-Russo et al., 2003). The order of activity (troglitazone>pioglitazone>rosiglitazone) is the reverse of their known PPARγ activity. Thiazolidinediones increase astrocyte cyclic AMP levels and their glucose effects were inhibited by protein kinase A inhibitors. Thiazolidinediones cause mitochondrial hyperpolarization. Pioglitazone has been shown to protect astrocytes from hypoglycemia-induced cell death (Dello-Russo et al., 2003). Because thiazolidinediones modify astrocyte glucose metabolism and mitochondrial function, they might be beneficial in neurological conditions where glucose availability is reduced.

The role of PPAR agonists in the treatment of human neurological disturbances is at the present time speculative. The presence of the various isoforms in brain cells and the few preliminary in vitro and in vivo animal studies that are available suggest that PPAR isoforms may play important regulatory roles in central nervous system function and that drugs that influence their functions may have utility. This area of research and its application to human disease is in its infancy.

Insulin resistance and its associated metabolic abnormalities contribute to the development of type 2 diabetes and cardiovascular disease. There are data to formulate the hypothesis that either insulin resistance or its presumed immediate cause (visceral adiposity) may be the underlying cause of the metabolic syndrome. It is likely that insulin resistance and the metabolic syndrome have pathophysiological impacts on other organs such as the central nervous system. Treatments directed at correcting insulin resistance are therefore appealing targets for the metabolic syndrome and perhaps a variety of other illnesses.

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