Improved Glucose Tolerance in Zucker Fatty Rats by Oral Administration of the Dipeptidyl Peptidase IV Inhibitor Isoleucine Thiazolidide

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The hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1 act on the pancreas to potentiate glucose-induced insulin secretion (enteroinsular axis). These hormones (incretins) are rapidly hydrolyzed by the circulating enzyme dipeptidyl peptidase IV (DP IV) into biologically inactive NH_2-terminally truncated fragments. This study describes the effect of inhibiting endogenous DP IV with a specific DP IV inhibitor, isoleucine thiazolidide (Ile-thiazolidide), on glucose tolerance and insulin secretion in the obese Zucker rat. In initial studies, the specificity of Ile-thiazolidide as an inhibitor of incretin degradation was determined using matrix-assisted laser desorption/ionization–time of flight mass spectrometry. These results showed that inhibiting DP IV activity with Ile-thiazolidide blocked the formation of NH_2-terminally truncated GIP and GLP-1. Oral administration of Ile-thiazolidide resulted in rapid inhibition of circulating DP IV levels by 65% in obese and lean Zucker rats. Suppression of DP IV levels enhanced insulin secretion in both phenotypes with the most dramatic effect occurring in obese animals (150% increase in integrated insulin response vs. 27% increase in lean animals). Ile-thiazolidide treatment improved glucose tolerance in both phenotypes and restored glucose tolerance to near-normal levels in obese animals. This was attributed to the glucose-lowering actions of increasing the circulating half-lives of the endogenously released incretins GIP and, particularly, GLP-1. This study suggests that drug manipulation of plasma incretin activity by inhibiting the enzyme DP IV is a valid therapeutic approach for lowering glucose levels in NIDDM and other disorders involving glucose intolerance. *Diabetes* 47:1253–1258, 1998

The term enteroinsular axis refers to the signaling pathways between the gut and pancreatic islets that amplify the insulin response to absorbed nutrients (1–3). Glucose-dependent insulinotropic polypeptide (GIP) and the truncated form of glucagon-like peptide-1 (GLP-1(7-36) amide) are considered to be the most important insulin-releasing hormones (incretins) comprising the enteroinsular axis (2–4). GIP and GLP-1 are members of the glucagon family of peptides and share considerable NH_2-terminal sequence identity, including alanine residues in position 2 from the NH_2-terminus. GIP and GLP-1(7-36) have been shown to be substrates of the circulating exopeptidase dipeptidyl peptidase IV (DP IV) (5–8), a peptidase that specifically cleaves the first two amino acids from peptides with an NH_2-terminal penultimate proline or alanine residue (9). The products of DP IV hydrolysis, GIP(3-42) and GLP-1(9-36), have been shown by us and others to lack insulinotropic activity (10–13). Numerous studies support the view that DP IV–mediated hydrolysis of these hormones is the primary mechanism of their inactivation in vivo (5–8).

The tripeptide Ile-Pro-Ile (diprotin A) acts as a competitive substrate of DP IV in vitro (14), and it has been shown to block DP IV–mediated incretin degradation in vitro (6,7). Diprotin A has not been effective in inhibiting DP IV levels in vivo, as this tripeptide serves as a substrate for DP IV and high concentrations (molar range) are required to inhibit circulating DP IV levels in the rat (R.A.P., R.P.P., unpublished observations). Ile-thiazolidide is a highly specific reversible competitive transition-state analog inhibitor of DP IV (K_i = 130 nmol/l) synthesized by H.-U.D. (9,15). We have recently demonstrated that matrix-assisted laser desorption/ionization–time of flight mass spectrometry (MALDI–TOF MS) is a highly sensitive and specific method to study the hydrolysis of GIP and GLP-1 by DP IV (8). In the present study, we have used this technique to investigate the effectiveness of Ile-thiazolidide as an inhibitor of DP-IV catalysis of these hormones.

The Zucker fatty rat exhibits abnormalities in glucose metabolism that characterize NIDDM, i.e., insulin secretory defects as well as insulin resistance (16,17) leading to hyperinsulinemia and glucose intolerance. Based on the known incretin-metabolizing actions of DP IV and the specificity of Ile-thiazolidide as a DP IV inhibitor, it was hypothesized that this compound could influence glucose tolerance in vivo by increasing the circulating half-lives of the incretins GIP and GLP-1. The use of an animal model of NIDDM was deemed appropriate given the effectiveness of exogenous GLP-1 as a glucose-lowering agent in NIDDM patients (18).

We first established that orally administered Ile-thiazolidide was effective in inhibiting circulating levels of DP IV in rats. We then undertook a study to determine the effect of DP IV inhibition by orally administered Ile-thiazolidide on glucose tolerance and insulin secretion in the fatty Zucker rat.

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DP IV, dipeptidyl peptidase IV; GIP, glucose-dependent insulinotropic polypeptide; GLP, glucagon-like peptide; MALDI–TOF MS, matrix-assisted laser desorption/ionization–time of flight mass spectrometry.

RESEARCH DESIGN AND METHODS

In vitro inhibition of DP IV by Ile-thiazolidide. Pooled human serum (20%) was incubated with GIP(1-42) (30 µmol/l) or GLP-1(7-36) (30 µmol/l) in 0.1 mmol/l Tricine buffer, pH 7.6, at 30°C in the presence or absence of 20 µmol/l Ile-thiazolidide. After a 21- to 24-h incubation, an equal volume of analyte and matrix (2′,6′-diydroxyacetophone) was combined, crystallized, and analyzed by MALDI-TOF MS as described by Pauly et al. (8). All spectra represent the cumulative sum of 250 single laser shots. Signals were quantified as relative amounts of GIP(1-42) or GLP-1(7-36): the net substrate peak height divided by the sum of the net substrate and product peak heights. Net peak heights were defined as peak height minus baseline.

Animals. A colony of Zucker rats was bred in the physiology department at the University of British Columbia. Age-matched groups (10–12 weeks) of obese (fatty) and lean animals of either sex were used. Fatty rats were homozygous (*fa*/*fa*), and lean animals were either *Fa*/*fa* or *Fa*/*Fa*. All experiments were carried out on conscious unrestrained rats.

Oral glucose tolerance test. After an overnight fast, lean or obese animals were administered oral glucose by syringe and feeding tube (1 g/kg) as a 40% solution (wt/vol). The DP IV inhibitor Ile-thiazolidide was dissolved in saline and administered along with the glucose at a dose of 20 µmol/l per 300 g body wt. In control experiments, saline was administered along with oral glucose. Blood samples were collected from the tail veins of conscious unrestrained rats into heparinized capillary tubes at 0 and 5, 10, 20, 30, and 60 min after glucose (glucose + Ile-thiazolidide) administration. Blood samples were centrifuged at 4°C, and DP IV activity was analyzed immediately. The remaining plasma was stored at –20°C until analysis for glucose and insulin measurement. Glucose levels were measured using the glucose oxidase procedure (Beckman glucose analyzer; Fullerton, CA). To determine whether Ile-thiazolidide had a direct effect on insulin secretion or fasting glucose levels (in the absence of glucose-stimulated incretin release), in one set of experiments, Ile-thiazolidide was administered orally with saline instead of glucose.

Assays. Insulin was measured by radioimmunoassay as described by Pederson et al. (19), using rat insulin as standard and a guinea pig anti-human insulin serum (GP01). Plasma DP IV activity was measured by a colorimetric assay. Gly-Pro-4-nitroanilide, a chromogenic substrate of DP IV, is hydrolyzed into the dipeptide Gly-Pro and the yellow product 4-nitroaniline, whose rate of appearance can be measured spectrophotometrically. The substrate consisted of 0.26 mmol/l Gly-Pro-nitroanilide (Sigma, St. Louis, MO) in 0.04 mol/l HEPES buffer. The assay mixture consisted of 270 µl of substrate and 30 µl plasma, and assays were carried out in 96-well microtiter plates. Optical density was measured at 0, 10, and 20 min by a Dynatech MRX Microplate Reader (Chantilly, VA) (wavelength 405 nm). DP IV activity is expressed as the change in optical density over 20 min.

Reagents. Ile-thiazolidide was synthesized in the laboratory of H.-U.D. (chemical structure Fig. 1*A*).

Statistical analysis. Comparisons between drug-treated and control rats were assessed by unpaired Student's t tests ($P < 0.05$ for significance).

RESULTS

In vitro inhibition of DP IV by Ile-thiazolidide. Incubation of 30 µmol/l GIP(1-42) in 20% human serum resulted in the hydrolysis of 71% of the native GIP into the reaction product GIP(3-42), as assessed by MALDI-TOF MS (Fig. 1*B*). Similarly, incubation of 30 µmol/l GLP-1(7-36) with serum for 21 h resulted in hydrolysis of 89.3% of the original peptide into the reaction product GLP-1(9-36) (Fig. 1*C*). Neither GIP(3-42) nor GLP-1(9-36) were detected in parallel experiments conducted under identical conditions but in the presence of 20 µmol/l Ile-thiazolidide.

Oral glucose tolerance in lean and obese Zucker rats. Figure 2*A* and *B* indicate that obese Zucker rats are hyperinsulinemic, exhibit fasting hyperglycemia (obese, 9.8 ± 0.33 mmol/l; lean, 7.5 ± 0.16 mmol/l; $P < 0.05$), and are glucose intolerant compared with lean age-matched control rats (peak values: obese, 19.2 ± 0.56 mmol/l; lean, 15.47 ± 0.32 mmol/l; $P < 0.05$).

In vivo inhibition of DP IV activity by Ile-thiazolidide. Oral administration of Ile-thiazolidide at a concentration of 20 µmol/l per 300 g body wt resulted in significant inhibition of circulating DP IV activity 5 min after oral administration (Figs. 3*A*, 4*A*, and 5*A*). Maximum inhibition was observed at time 30 min (65% suppression). Preliminary experiments indicate that plasma DP IV activity returns to pretreatment levels after 12–14 h in both lean and obese animals (data not shown).

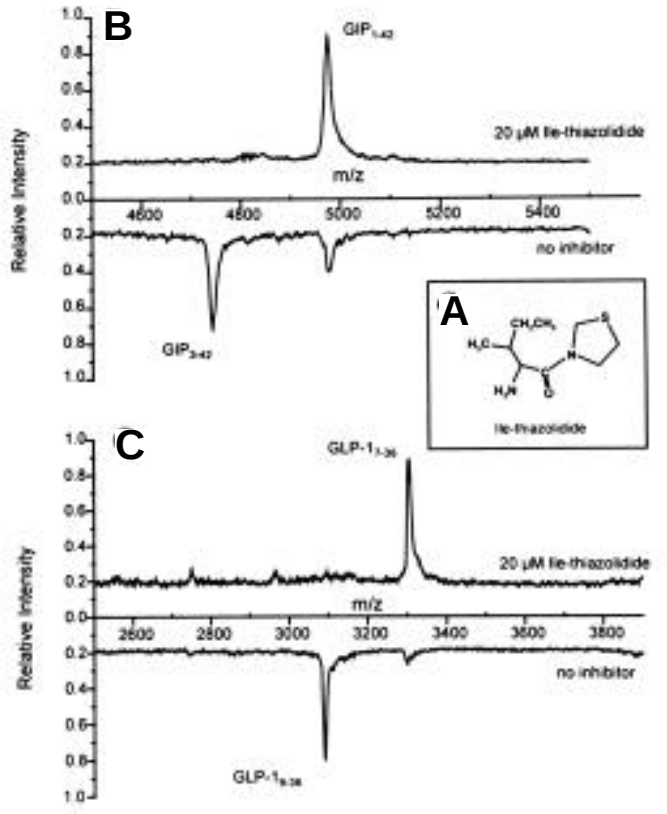

FIG. 1. MALDI–TOF MS analysis of GIP(1-42) (30 µmol/l) (*B*) and GLP-1(7-36) (30 µmol/l) (*C*) degradation by serum DP IV in the presence or absence of 20 µmol/l Ile-thiazolidide. Signals of the intact hormone peaks [GIP(1-42) and GLP-1(7-36)] and the NH_2-terminally truncated DP IV reaction products [GIP(3-42) and GLP-1(9-36)] are identified. *A*: The structure of Ile-thiazolidide.

Effect of Ile-thiazolidide on glucose tolerance in lean and obese Zucker rats. Figures 3 and 4 show the glucose and insulin responses to an oral glucose challenge in lean and obese Zucker rats, respectively, in the presence or absence of oral Ile-thiazolidide. Figures 3*A* and 4*A* show plasma DP IV activity in the presence or absence of oral Ile-thiazolidide. Figures 3–5 insets show integrated insulin and glucose responses to an oral glucose challenge. In both lean and obese animals, suppression of DP IV levels enhanced the insulin response to oral glucose and improved glucose tolerance. The insulin secretory response to oral glucose was greater in the presence of Ile-thiazolidide in both lean and obese rats. The increase in integrated insulin response resulting from inhibition of circulating DP IV was greater in obese than in lean animals (Figs. 3*B* and 4*B* insets). The integrated insulin response to only glucose in the presence of Ile-thiazolidide in obese rats was 150% greater than that in control rats compared with a 27% increase in lean animals. The improvement in glucose tolerance was also more dramatic in obese compared with lean animals after oral Ile-thiazolidide treatment, with a 39% decrease in integrated glucose compared with a 22% reduction after Ile-thiazolidide treatment of lean animals (Figs. 3*C* and 4*C*). This was most evident at time 60 min when glucose levels were 35% lower in obese Ile-thiazolidide–treated animals compared with nontreated

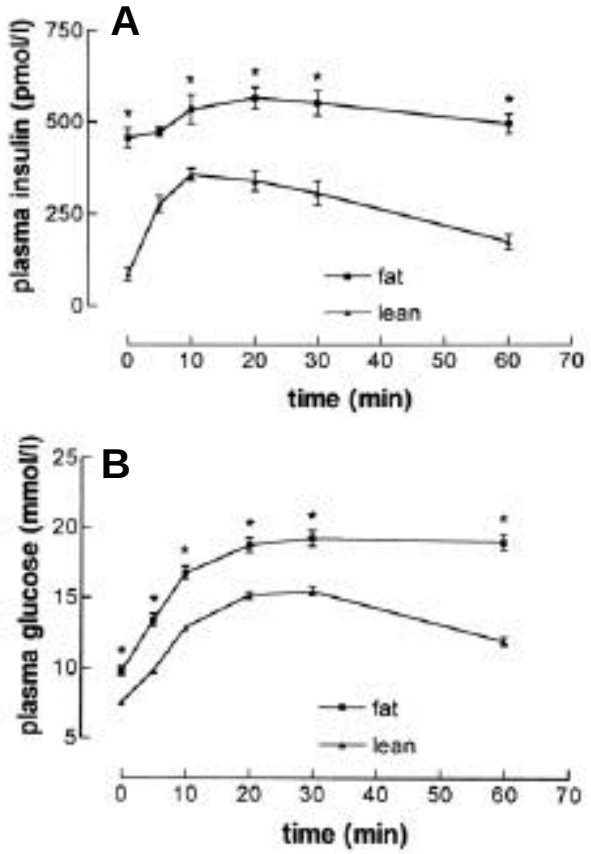

FIG. 2. Insulin (*A*) and glucose (*B*) responses to 1 g/kg oral glucose in lean (*n* = 6) and obese (*n* = 6) Zucker rats. *Significance to at least the 0.05 level.

obese control rats (19.0 ± 0.5 vs. 12.5 ± 0.37 mmol/l), whereas plasma glucose levels in treated versus nontreated lean animals were not significantly different at this time period (10.7 ± 0.4 vs. 11.9 ± 0.3 mmol/l) (Fig. 2*C*).

Effect of Ile-thiazolidide on fasting glucose and insulin levels in obese Zucker rats. Ile-thiazolidide was administered in the absence of glucose to determine if the improvement in glucose tolerance in the obese Zucker rat was due to a direct glucose-lowering action of the drug. Figure 5 indicates that oral Ile-thiazolidide did not alter fasting glucose or insulin levels in the absence of endogenous incretin release.

DISCUSSION

The circulating enzyme DP IV inactivates the circulating incretins GIP and GLP-1 by cleaving the NH_2-terminal dipeptide from both molecules. It has been shown by us and others that this occurs very rapidly in plasma and undoubtedly plays a regulatory role in the enteroinsular axis (5–8).

We have previously demonstrated that circulating DP IV rapidly metabolizes GIP(1-42) and GLP-1(7-36) to the truncated forms GIP(3-42) and GLP-1(9-36) in vivo (6). Because NH_2-terminal truncation destroys the insulin-releasing actions of both incretins (10–13), it was hypothesized that inhibition of plasma DP IV would result in improved glucose tolerance by an incretin-mediated mechanism (prolonging the circulating half-life of intact biologically active GIP and GLP-1). Because GLP-1 has gained considerable importance as a glucose-lowering drug in NIDDM (18,20,21), it was of interest to determine the effectiveness of altering the circulating half-life of this hormone in an animal model of NIDDM, the obese Zucker rat. That obese Zucker rats from our colony fulfill the criteria of insulin resistance, as well as fasting hyperglycemia and glucose intolerance, is indicated in Fig. 2. The aims of the current study were twofold: *1*) to determine the effectiveness of orally administered Ile-thiazolidide as an inhibitor of circulating DP IV activity and *2*) to assess the effect of DP IV inhibition on the enteroinsular axis in the fatty Zucker rat.

In an initial study to characterize the activity of Ile-thiazolidide on incretin metabolism, MALDI-TOF MS was used to investigate the effect of DP IV inhibitor Ile-thiazolidide on the in vitro degradation of GIP(1-42) and GLP-1(7-36) after incubation in human serum. Results presented in Fig. 1 indicate that DP IV is the principal serum protease responsible for the degradation of GIP(1-42) and GLP-1(7-36) into the inactive polypeptides GIP(3-42) and GLP-1(9-36), since the presence of Ile-thiazolidide, a highly specific inhibitor of DP IV, was able to completely block the formation of the DP IV reaction products during the 21- to 24-h incubation.

Oral administration of Ile-thiazolidide resulted in prompt (within 5 min) inhibition of circulating DP IV activity with maximum suppression (65%) occurring 30 min after ingestion (Figs. 3*A*, 4*A*, and 5*A*). When administered with oral glucose, Ile-thiazolidide resulted in a significantly greater insulin response and attendant improvement in glucose tolerance in both lean and obese Zucker rats (Figs. 3 and 4). The degree of enhancement of the integrated insulin response to oral glucose resulting from DP IV inhibition was greater in obese than in lean animals (Figs. 3*B* and 4*B*), and the pattern of insulin secretion after DP IV inhibition differed in fat compared with lean animals. The greatest difference in insulin secretion between treated and untreated lean animals occurred 10 min after oral glucose in the presence of Ile-thiazolidide. The finding that insulin levels do not remain elevated in the DP IV–inhibited lean rats, despite an increase in the half-life of endogenously released incretins, implies the existence of a mechanism that prevents the secretion of inappropriate amounts of insulin (even in the presence of elevated levels of intact GIP and GLP-1). An explanation for falling insulin levels in the presence of elevated incretin concentrations would undoubtedly involve the concomitant reduction in plasma glucose, as both incretins stimulate insulin in a glucose-dependent manner (2–4). In the case of obese animals, the enhanced insulin response to Ile-thiazolidide occurred throughout the 60-min sampling period. A possible explanation for this observation is the impaired islet function in these animals; however, a contributing factor may also be the lack of a glucose threshold for the insulinotropic actions of both GIP and GLP-1 in the *fa/fa* rat (22,23). Long-acting incretins may exert a more prolonged insulinotropic action in animals lacking the normal self-regulating glucose threshold possessed by lean (normal) animals. The glucose-lowering actions of DP IV suppression are more dramatic in obese compared with lean rats (Figs. 3*C* and 4*C*), as one would predict from the greater insulin response in drug-treated obese animals. In Ile-thiazolidide–treated obese rats, the glucose tolerance curve resembled that of the lean phenotype. At the 60-min interval, untreated obese animals exhibited near-peak glucose values (19 mmol/l) compared with a 35%

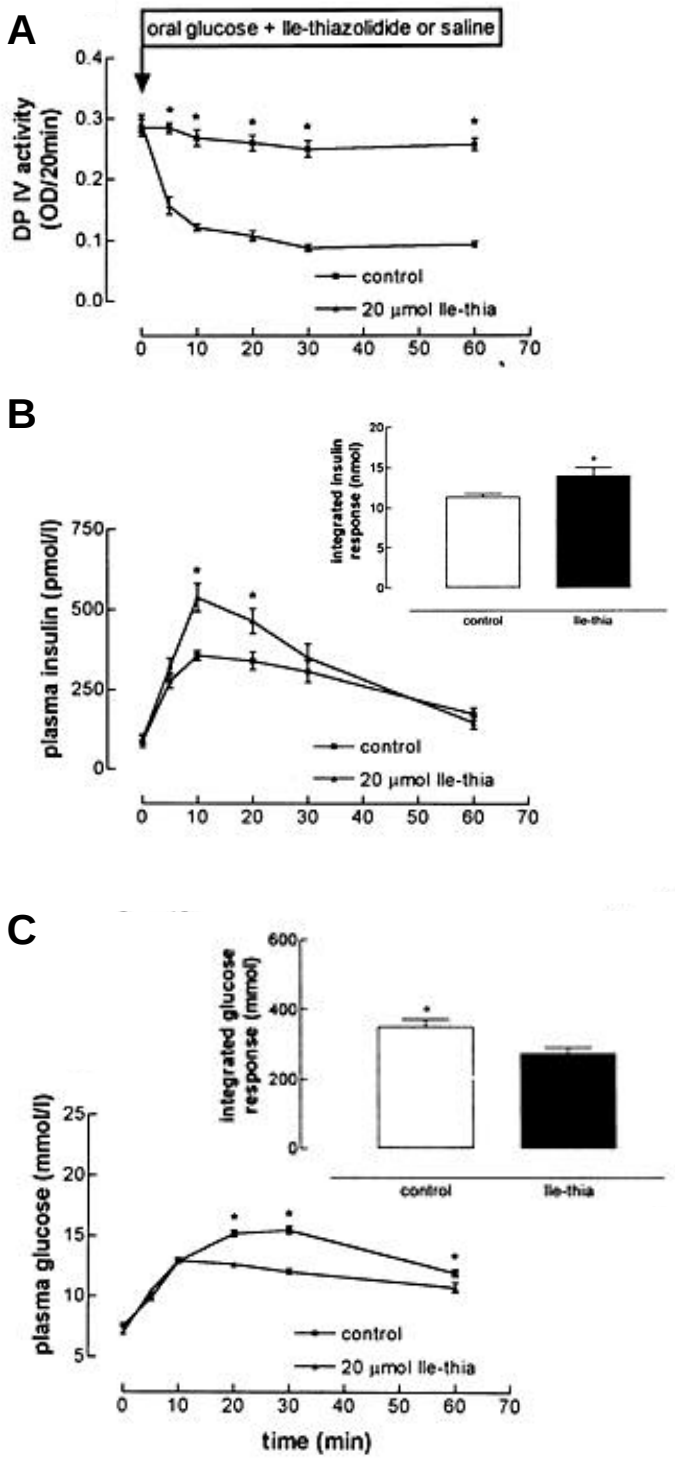

FIG. 3. The effect of oral administration of Ile-thiazolidide on plasma DP IV activity (*A*) and the insulin (*B*) and glucose (*C*) responses to oral glucose in lean Zucker rats (*n* = 6 for each group). Insets represent integrated responses. *Significance to at least the 0.05 level.

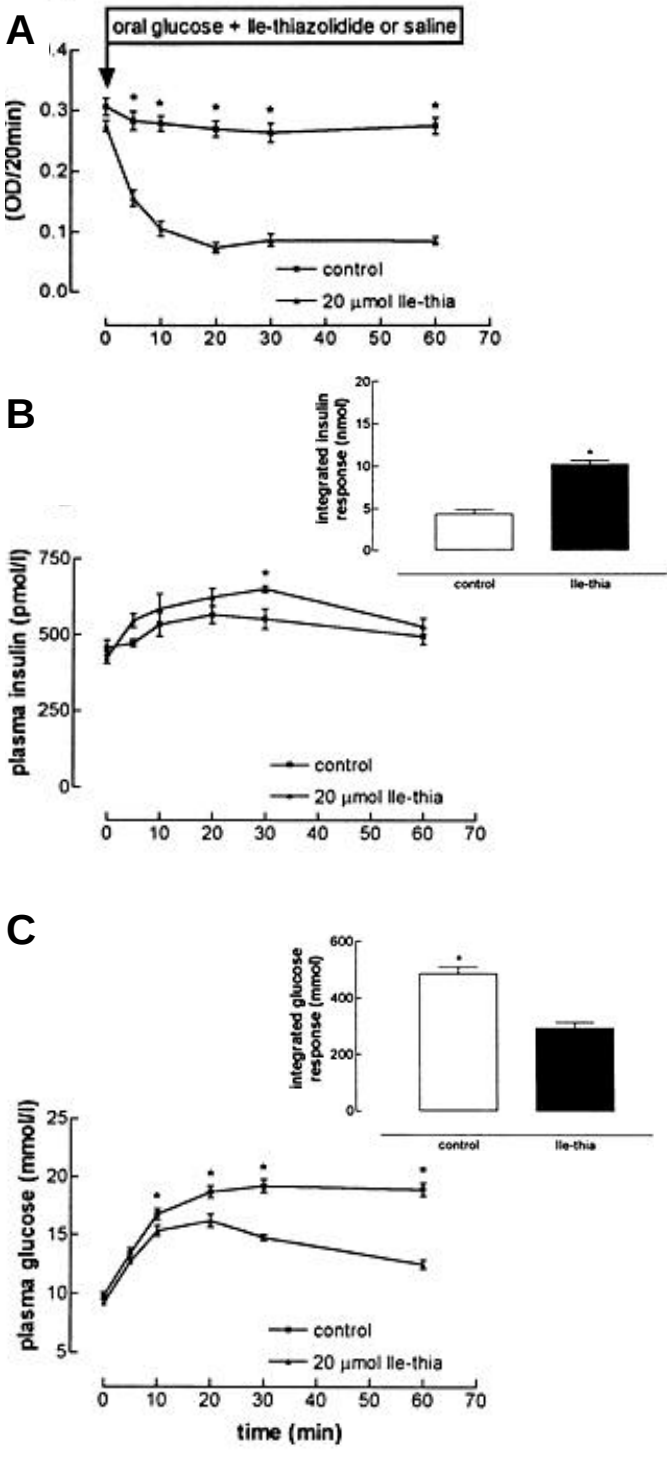

FIG. 4. The effect of oral administration of Ile-thiazolidide on plasma DP IV activity (*A*) and the insulin (*B*) and glucose (*C*) responses to oral glucose in obese Zucker rats (*n* = 6 for each group). Insets represent integrated responses. *Significance to at least the 0.05 level.

decrease in Ile-thiazolidide–treated *fa*/*fa* animals (12.5 mmol/l). The glucose-lowering effects of suppressing circulating DP IV with Ile-thiazolidide may stem from the insulin-independent glucose-lowering actions of intact circulating GLP-1 as well as enhancing the insulin-releasing actions of GIP and GLP-1 (24–28). The effectiveness of GLP-1 as a glucose-lowering agent in NIDDM patients has been attributed to the potent suppression of glucagon secretion and inhibition of gastric emptying as well as enhanced insulin secretion. These factors, as well as increased insulin secretion, may con-

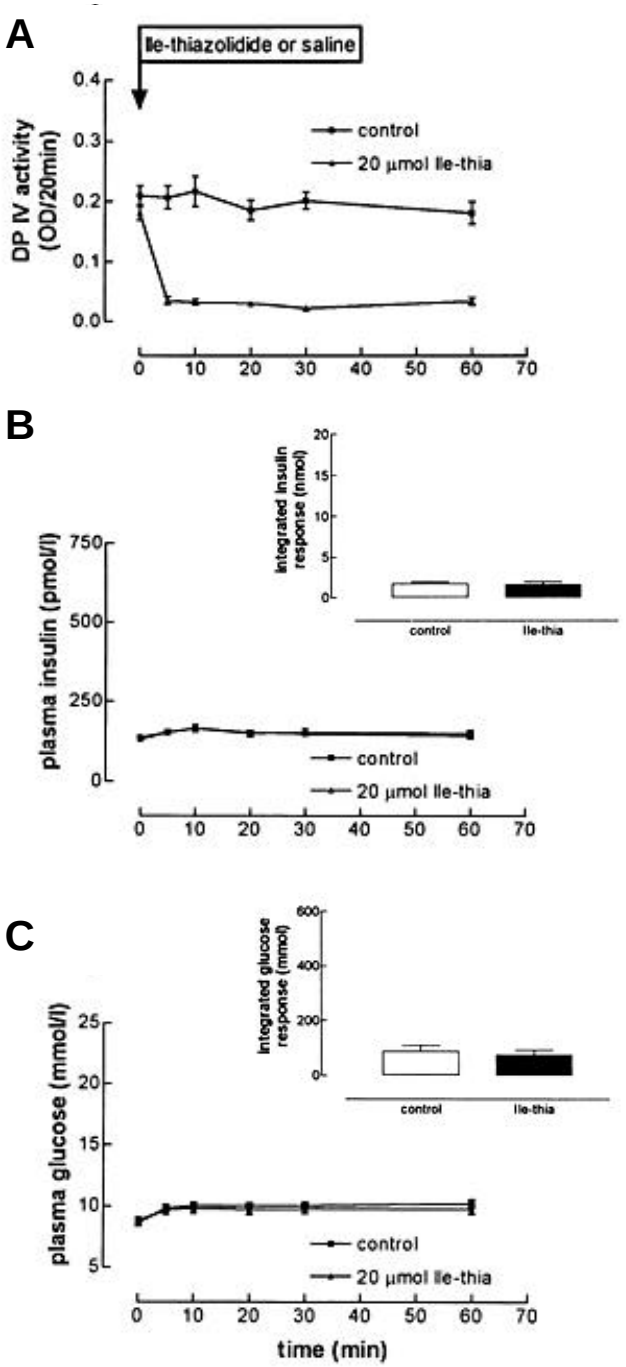

FIG. 5. The effect of oral administration of Ile-thiazolidide on plasma DP IV activity (*A*) and fasting insulin (*B*) and glucose (*C*) levels in obese Zucker rats (*n* = 6 for each group). Insets represent integrated responses.

tribute to the greater glucose-lowering action of DP IV inhibition in obese compared with lean rats, considering that glucagon levels are exaggerated in obese Zucker rats (29). Disadvantages of incretin therapy are the rapid metabolism of exogenously administered native peptides in the circulation and ineffectiveness of oral administration. Inhibition of the incretin-inactivating enzyme DP IV by an oral drug overcomes both these problems. To determine whether the DP IV inhibitor Ile-thiazolidide had direct glucose-lowering actions, it was administered orally without glucose to fasted obese rats. Results presented in Fig. 5 indicate that Ile-thiazolidide neither lowered fasting glucose nor enhanced insulin levels in obese rats, in the absence of glucose-stimulated incretin release. This lends support to the hypothesis that this drug increases insulin secretion and improves oral glucose tolerance by inhibiting the degradation of GIP and GLP-1 by the circulating enzyme DP IV, i.e., by an incretin-mediated mechanism. DP IV also plays a role in the inactivation of regulatory peptides (other than the incretins) that possess proline or alanine residues in the penultimate NH_2-terminal position. Examples are growth hormone–releasing hormone, neuropeptide Y, peptide YY, and prolactin (9). The effect of short-term inhibition of circulating DP IV activity on the actions of these peptides is as yet unknown. Regarding the possible toxicity of Ile-thiazolidide, no deleterious effects have been noted on long-term cell culture (9) or after 5 days of oral treatment in rats (H.A.W., R.A.P., unpublished observations).

In summary, inhibition of circulating DP IV enhanced insulin secretion and improved glucose tolerance in response to an oral glucose challenge in lean and obese fatty (*fa/fa*) rats. The enhanced incretin response was greater in obese than in lean animals, with a more profound improvement in glucose tolerance by Ile-thiazolidide. This was attributed to disruption of DP IV inactivation of GIP and GLP-1, resulting in amplification of the enteroinsular axis. These data support a therapeutic approach of drug manipulation of plasma incretin activity for lowering glucose levels in NIDDM and other disorders involving glucose intolerance.

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