Higher fasting plasma concentrations of glucagon-like peptide 1 are associated with higher resting energy expenditure and fat oxidation rates in humans\(^1\)–\(^3\)

Nicola Pannacciulli, Joy C Bunt, Juraj Koska, Clifton Bogardus, and Jonathan Krakoff

**ABSTRACT**

**Background:** Glucagon-like peptide 1 (GLP-1) is a gut hormone that decreases appetite and promotes satiety. Its role in energy metabolism regulation is still poorly understood.

**Objective:** The aim of the study was to investigate the relation of fasting plasma GLP-1 concentrations to rates of energy expenditure (EE) and substrate oxidation—ie, respiratory quotient (RQ).

**Design:** Forty-six glucose-tolerant white subjects (22 men, 24 women) aged 18–49 y whose adiposity spanned a wide range [body mass index (in kg/m\(^2\)): 18.5–50] were studied in an inpatient clinic. Main outcome measures included resting EE and RQ (ventilated hood technique), body composition (dual-energy X-ray absorptiometry), and fasting plasma concentrations of GLP-1, pancreatic polypeptide, glucose, and insulin.

**Results:** Fasting plasma GLP-1 concentrations were positively associated with resting EE (after adjustment for age, sex, and body composition) and negatively correlated with RQ (after adjustment for age, sex, and percentage body fat) and fasting plasma pancreatic polypeptide concentrations (both before and after adjustment for age, sex, percentage body fat, and fasting plasma glucose and insulin concentrations). Adjustment for fasting plasma pancreatic polypeptide concentrations, a marker of parasympathetic outflow to the gut, attenuated the strength of the association of fasting plasma GLP-1 concentrations with resting EE and RQ.

**Conclusions:** Higher fasting plasma GLP-1 concentrations are associated with higher rates of EE and fat oxidation independent of age, sex, and body composition. The autonomic nervous system may have a role in this relation. This effect, along with the established role of GLP-1 in promoting satiety, may further foster its therapeutic potential in the treatment of obesity. Am J Clin Nutr 2006;84:556–60.

**KEY WORDS** Glucagon-like peptide 1, GLP-1, energy expenditure, substrate oxidation

**INTRODUCTION**

Glucagon-like peptide 1 (GLP-1) is a gut peptide that is secreted by the intestinal L cells in response to nutrient ingestion through both direct and neurally mediated mechanisms (1). GLP-1’s biological actions are multifaceted and include effects on glucose-dependent insulin secretion, insulin biosynthesis, islet \(\beta\)-cell neogenesis, gastrointestinal motility, neuronal plasticity, and food intake (1). When administered intracerebroventricul-}

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\(^1\) From the Obesity and Diabetes Clinical Research Section, Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Phoenix, AZ.

\(^2\) Supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

\(^3\) Reprints not available. Address correspondence to N Pannacciulli, ODRC/PECRB/NIDDK/NIH/DHHS, 4212 North 16th Street, Phoenix, AZ 85016. E-mail: nicolap@mail.nih.gov.

Received November 3, 2005.

Accepted for publication May 9, 2006.
with an increase in EE (4). Whether a relation between GLP-1 and REE exists in humans has yet to be established.

To test the hypothesis that GLP-1 is related to REE and substrate oxidation rates in humans, we measured fasting plasma concentrations of GLP-1 in 46 white men and women with normal glucose tolerance who underwent indirect calorimetry with the use of the ventilated hood technique to measure REE and substrate oxidation. Fasting plasma concentrations of pancreatic polypeptide (PP), a valid surrogate marker of the parasympathetic drive to the pancreas (14), were also measured to take into account the well-established interaction between the parasympathetic nervous system and GLP-1 (15, 16).

SUBJECTS AND METHODS

Subjects

The subjects, 22 white men and 24 white women aged 18–49 y, were recruited by using newspaper advertisements in the Phoenix, AZ, metropolitan area (Table 1), as part of a larger study of neuroanatomical correlates of eating behavior (17, 18). All of the subjects reported that they were nonsmokers and not taking any medications. All were in good health, as assessed by physical examination and laboratory tests. The female volunteers were studied while in the follicular phase of the menstrual cycle.

Subjects were admitted for 1 wk to the Obesity & Diabetes Clinical Research Section of the National Institutes of Health (Phoenix). Subjects were restricted to the metabolic ward, placed on a weight-maintenance diet (50% of energy as carbohydrate, 30% of energy as fat, and 20% of energy as protein), and limited to sedentary activity for the duration of the study. Three days after admission and after a 12-h overnight fast, subjects underwent a 2-h 75-g oral-glucose-tolerance test to exclude impaired glucose tolerance and diabetes. During the imaging session, blood samples for metabolic measurements were collected before the administration of a satiating amount of a liquid formula meal (Ensure Plus, 1.5 kcal/mL; Ross-Abbott Laboratories, Columbus, OH) that provides 50% of a person’s measured REE, as described previously (17, 18). Fasting plasma concentrations of both GLP-1 and PP represent the average of 2 samples collected 10 min apart before the administration of the meal.

Written informed consent was obtained from all subjects. The protocol was approved by the institutional review boards of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK-NIH) and the Banner Good Samaritan Medical Center (Phoenix, AZ), where the imaging session took place.

Statistical analysis

Statistical analyses were performed by using SAS statistical software (version 8.2; SAS Institute, Cary, NC). On the basis of results from previous studies (19, 20), REE was adjusted for age, sex, FFM, and FM, whereas RQ was adjusted for age, sex, and percentage body fat (%BF) by using general linear regression modeling before correlation analyses. A stepwise multiple regression approach was used to calculate the amount of variance in REE and RQ explained by fasting plasma GLP-1 concentrations. The relations of fasting plasma GLP-1 concentrations with adjusted REE and RQ and the other study variables were examined by using Pearson correlation analysis. Partial correlation coefficients were used to account for the effects of age, sex, %BF, and other metabolic variables on the relation between fasting plasma concentrations of GLP-1 and PP.

RESULTS

Fasting plasma GLP-1 concentrations were positively correlated with REE after adjustment for age, sex, FFM, and FM (r = 0.41, P = 0.004; Figure 1) and negatively associated with RQ after adjustment for age, sex, and %BF (r = −0.40, P = 0.007; Figure 2). The associations of fasting plasma GLP-1 concentrations with adjusted REE and RQ did not change after the exclusion of potential outliers (data not shown). In particular, fasting plasma GLP-1 concentrations accounted for an additional 6% of the variance in REE after adjustment for age, sex, FFM, and FM (Table 2). Similarly, fasting plasma GLP-1 concentrations accounted for 9% of the variance in RQ after adjustment for age, sex, and %BF (Table 3).

The plasma GLP-1 concentrations measured 30 min after the initiation of a liquid formula meal were positively associated with adjusted REE and negatively correlated with adjusted RQ, although the significance of these associations was attenuated (data not shown). Nonetheless, when fasting plasma GLP-1 concentrations were accounted for, the correlations of postprandial

### Table 1

Characteristics of the study subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (y)</td>
<td>32 ± 8 (18–49)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>92 ± 26 (50–140)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32 ± 9 (18.5–50)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>29 ± 10 (7–44)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>4.5 ± 0.5 (3.1–6.1)</td>
</tr>
<tr>
<td>Fasting plasma insulin (pmol/L)</td>
<td>132 ± 42 (42–168)</td>
</tr>
<tr>
<td>Fasting plasma GLP-1 (pmol/L)</td>
<td>22.8 ± 6.7 (7.6–36.5)</td>
</tr>
<tr>
<td>Fasting plasma PP (pmol/L)</td>
<td>14.5 ± 15.0 (1.5–82.0)</td>
</tr>
<tr>
<td>REE (kcal/d)</td>
<td>1608 ± 362 (1091–2835)</td>
</tr>
<tr>
<td>RQ</td>
<td>0.88 ± 0.05 (0.71–0.98)</td>
</tr>
</tbody>
</table>

All values are ± SD; range in parentheses. n = 46. GLP-1, glucagon-like peptide 1; PP, pancreatic polypeptide; REE, resting energy expenditure; RQ, respiratory quotient.
plasma GLP-1 concentrations with adjusted REE and adjusted RQ were no longer significant, and the postprandial plasma GLP-1 concentrations did not affect the associations of fasting plasma GLP-1 concentrations with either adjusted REE or adjusted RQ, which remained the same after adjustment for the postprandial plasma GLP-1 concentrations.

Fasting plasma concentrations of GLP-1 and PP were negatively correlated both before \((r = -0.50, P = 0.0002)\) and after (partial \(r = -0.58, P < 0.0001\)) adjustment for age, sex, %BF, and fasting plasma concentrations of glucose and insulin (Figure 3). The association between fasting plasma GLP-1 and PP concentrations did not change after the exclusion of potential outliers (data not shown).

When the correlations of fasting plasma GLP-1 concentrations with adjusted REE (age, sex, FFM, and FM) and adjusted RQ (age, sex, and %BF) were further adjusted for fasting plasma PP concentrations, the strength of these associations was attenuated \((r = 0.30, P = 0.05)\) and \(r = -0.30, P = 0.05)\), respectively. No correlations were found between fasting plasma GLP-1 concentrations and the other general, anthropometric, and metabolic variables, including glucose and insulin (data not shown).

**DISCUSSION**

In the current study, fasting plasma GLP-1 concentrations were independently associated with REE (positively) and RQ (negatively) in glucose-tolerant subjects. Furthermore, we reported a negative association between fasting plasma concentrations of GLP-1 and PP, which is considered a valid marker of parasympathetic drive to the gastrointestinal system.

The current findings are consistent with animal studies showing greater oxygen consumption, an index of EE, in response to the central and peripheral administration of GLP-1 (4, 5), in that fasting plasma GLP-1 concentrations were found to be positively associated with REE and to explain a significant proportion of REE’s variance above and beyond that accounted for by the major predictors of this metabolic variable—ie, age, sex, and body composition (21). These results point to an important role of GLP-1 in the regulation of energy metabolism in humans.

The positive association between fasting GLP-1 plasma concentrations and REE only apparently contrasts with the previously reported negative effect of GLP-1 on diet-induced thermogenesis in humans (7, 8). In fact, the latter action may be due to the effect of this gut hormone on gastrointestinal motility, mostly consisting of a slowing of gastric emptying (9, 15), rather than to GLP-1 itself. An increase in EE in response to GLP-1 infusion has been reported in humans during the hyperglycemic clamp (6). However, this effect apparently was mediated by GLP-1–induced stimulation of insulin secretion, because it was no longer present when plasma insulin concentrations were kept constant by somatostatin infusion (6). Nevertheless, rats with streptozotocin-induced diabetes had an increase in thermogenesis after GLP-1 administration, which indicated no significant contribution of insulin (5). In addition, mice lacking dipeptidyl peptidase IV, an endogenous enzyme involved in the metabolic inactivation of GLP-1, have higher EE than do mice with dipeptidyl peptidase IV (22). Similarly, intravenous administration of GLP-1 induced dose-dependent increases in metabolic rate in rats (5).

The thermogenic effect of GLP-1 in the above studies was accompanied by tachycardia, which pointed to an activation of the sympathoadrenal system (5). In fact, both intravenous and

### Table 2

Predictors of resting energy expenditure

<table>
<thead>
<tr>
<th>Covariates</th>
<th>(\beta)</th>
<th>(P)</th>
<th>(R^2) (stepwise approach)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3.0</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>Male sex</td>
<td>-81.4</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>Fat-free mass</td>
<td>24.1</td>
<td>&lt;0.0001</td>
<td>0.68</td>
</tr>
<tr>
<td>Fat mass</td>
<td>-0.1</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>Glucagon-like peptide 1</td>
<td>3.0</td>
<td>0.005</td>
<td>0.06</td>
</tr>
</tbody>
</table>

\(n = 46). Linear regression modeling was used.

### Table 3

Predictors of respiratory quotient

<table>
<thead>
<tr>
<th>Covariates</th>
<th>(\beta)</th>
<th>(P)</th>
<th>(R^2) (stepwise approach)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.01</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>Male sex</td>
<td>-0.04</td>
<td>0.02</td>
<td>0.07</td>
</tr>
<tr>
<td>Body fat</td>
<td>-0.01</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>Glucagon-like peptide 1</td>
<td>-0.01</td>
<td>0.03</td>
<td>0.09</td>
</tr>
</tbody>
</table>

\(n = 46). Linear regression modeling was used.
intracerebroventricular administration of GLP-1 receptor agonists increased blood pressure and heart rate by activating autonomic regulatory sites in the rat brain (13). Similarly, we recently reported a positive association between GLP-1 and sympathetic nervous system activity in the postprandial state in humans (23).

It was recently shown that GLP-1 concentrations after weight loss were lower than those before weight loss in overweight or obese subjects (24). Therefore, in the light of the positive association between fasting plasma GLP-1 concentrations and REE adjusted for sex, age, and body composition, lower GLP-1 concentrations after weight loss may help explain the lower rates of EE that occur in response to weight reduction (25).

The negative correlation between fasting plasma GLP-1 concentrations and RQ is consistent with previous reports of a GLP-1–induced reduction in carbohydrate oxidation after a meal in lean and obese humans given GLP-1 intravenously (7, 8). However, this effect was measured in relation to food ingestion and may have been influenced by the GLP-1–induced slowing of gastric emptying, which led to a reduction in the meal-related insulin response. We report an independent relation between endogenous GLP-1 and substrate metabolism, which indicates a positive effect of this gut peptide on fat oxidation, a negative effect on carbohydrate oxidation, or both. This effect of GLP-1 is likely to be mediated by the sympathetic nervous system, whose activation is known to stimulate lipolysis and fatty acid oxidation (26).

The negative association between GLP-1 and PP is likely to reflect the complex interaction between this incretin and the parasympathetic outflow to the gut, of which PP plasma concentrations are a valid surrogate marker (14). In this respect, it has been suggested that intrinsic enteric cholinergic nerves regulate GLP-1 secretion in pigs and that the extrinsic parasympathetic innervations have little effect (16). In addition, subcutaneous or intravenous infusion of GLP-1 dose-dependent and reversibly inhibited PP release in response to a meal, and these effects were lost after abdominal vagotomy (27), which points to an inhibition of efferent parasympathetic function. Of note, the effect of GLP-1 on the PP response to food ingestion is independent of gastric emptying (29), which indicates a direct reciprocal relation between these 2 hormones, regardless of their dynamic changes after a meal.

The inhibitory effect of peripheral GLP-1 on parasympathetic outflow is exerted via interaction with centers in the brain or afferent neural pathways that are being relayed to the vagal motor nuclei (28). Similarly, the thermogenic effect of GLP-1 is mediated by its action on sympathetic control sites that are located mainly in the lower brainstem but also at the peripheral ganglia (5). Therefore, a complex interaction of GLP-1 with the autonomic nervous system, including inhibition of parasympathetic and stimulation of sympathetic drive, may explain the current findings of a relation of GLP-1, PP, EE, and substrate oxidation.

In conclusion, the current study shows that higher fasting plasma GLP-1 concentrations are associated with higher rates of EE and fat oxidation (or lower levels of carbohydrate oxidation, or both) independently of age, sex, and body composition. This effect, along with the established role of GLP-1 in decreasing appetite and promoting satiety in both animal models and humans (30), may further foster GLP-1’s therapeutic potential in both the treatment of type 2 diabetes (31) and the management of obesity.

We thank the nursing and dietary staffs, physician assistants, and lab technicians of the clinical research center for their valuable assistance. We are especially grateful to Mark L. Heiman (Eli Lilly Co, Indianapolis, IN) for his careful and accurate measurements of the gut peptides and to the subjects who volunteered for this study. We are grateful to Jeffrey Curtis (Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, for critical review of the manuscript.

NP planned the study, collected and analyzed data, and wrote the report. JCB, JK, CB, and JAK helped analyze data and write the report. None of the authors had a personal or financial conflict of interest.

REFERENCES


