Glucagon-like peptide-1 reduces hepatic glucose production indirectly through insulin and glucagon in humans

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ABSTRACT

The effect of glucagon-like peptide-1 (GLP-1) on hepatic glucose production and peripheral glucose utilization was investigated with or without infusion of somatostatin to inhibit insulin and glucagon secretion in 13 healthy, non-diabetic women aged 59 years. After 120 min 3-3H-glucose infusion, GLP-1 was added (4.5 pmol kg\(^{-1}\) bolus + 1.5 pmol kg\(^{-1}\) min\(^{-1}\)). Without somatostatin (\(n = 6\)), GLP-1 decreased plasma glucose (from 4.8 ± 0.2 to 4.2 ± 0.3 mmol L\(^{-1}\), \(P = 0.007\)). Insulin levels were increased (48 ± 3 vs. 243 ± 67 pmol L\(^{-1}\), \(P = 0.032\)), as was the insulin to glucagon ratio (\(P = 0.044\)). The rate of glucose appearance (\(R_a\)) was decreased (\(P = 0.003\)) and the metabolic clearance rate of glucose (MCR) was increased during the GLP-1 infusion (\(P = 0.024\) vs. saline). Also, the rate of glucose disappearance (\(R_d\)) was reduced during the GLP-1 infusion (\(P = 0.004\)). Since \(R_a\) was reduced more than \(R_d\), the net glucose flow was negative, which reduced plasma glucose.

Somatostatin infusion (500 \(\mu\)g h\(^{-1}\), \(n = 7\)) abolished the effects of GLP-1 on plasma glucose, serum insulin, insulin to glucagon ratio, \(R_a\), \(R_d\), MCR and net glucose flow. The results suggest that GLP-1 reduces plasma glucose levels mainly by reducing hepatic glucose production and increasing the metabolic clearance rate of glucose through indirectly increasing the insulin to glucagon ratio in healthy subjects.

Keywords GLP-1, glucose metabolic clearance rate, rate of glucose appearance, rate of glucose disappearance, somatostatin.

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The mechanism underlying the reduction in plasma glucose caused by GLP-1 has not been established. Theoretically, it could be due to direct or indirect effects through changes in circulating insulin and glucagon, and it could be attributed to decreased hepatic glucose output and/or increased peripheral glucose uptake. It seems established that GLP-1 infusion decreases hepatic glucose output as shown in both humans and rats (Hvidberg et al. 1994, van Dijk et al. 1996), thereby reducing plasma glucose levels. It is not known, however, whether this effect of GLP-1 on hepatic glucose production is due to a direct effect of GLP-1 on the liver, or whether the effect is mediated indirectly through the changes in insulin and glucagon levels. Furthermore, the possible effects of GLP-1 on....
peripheral glucose uptake are even less clear. One study in IDDM subjects suggested that GLP-1 increases insulin sensitivity as measured with the hyperinsulinaemic, euglycaemic clamp (Gutniak et al. 1992). Another study using the IVGTT with minimal model assessment suggested an increased insulin-independent glucose uptake during GLP-1 infusion (D'Alessio et al. 1994). In contrast to this, the glucose rate of disappearance was unchanged by GLP-1 when measured using infusion of 3-3H-glucose in rats and humans (Hvidberg et al. 1994, van Dijk et al. 1996). Thus, the effects and mechanisms of GLP-1 on glucose turnover need further evaluation. Therefore, we measured the rate of glucose appearance and disappearance using the 3-3H-glucose tracer technique. Two series of experiments were performed. In the first series, GLP-1 or saline was infused after a 2 h tracer equilibration period. In the second series, insulin and glucagon secretion were inhibited with concomitant somatostatin infusion, while the tracer and GLP-1/saline infusions were the same as in the first series. This design enabled evaluation of the effects of GLP-1 on hepatic glucose production and peripheral glucose uptake in healthy subjects, and also allowed the determination of whether these effects are direct effects of GLP-1 or are indirectly mediated through changes in circulating insulin and glucagon levels.

**METHODS**

**Subjects**

We studied 13 women aged 59 years. They were all non-diabetic according to a 75 g oral glucose tolerance test using WHO criteria (WHO 1985), and had normal liver and thyroid function tests at the entry in the study. None were taking any medication known to affect glucose tolerance. Clinical characteristics of the study subjects are shown in Table 1. All subjects received oral and written information concerning the aims and methods, and signed a consent declaration before the start of the study. The study protocol was approved by the ethics committee of Lund University.

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**GLP-1**

Synthetic human GLP-1 (GLP-1(7–36)amide = proglucagon(78–107)amide) was purchased from Peninsula Laboratories Europe, Meyerside, UK. The same lot number was used in all studies. The peptide was dissolved in sterile 0.9% saline solution containing 1% human serum albumin and filtered through a 0.22 μm nitrocellulose filter (Millex GV, Millipore, Bedford, Mass., USA) and stored at −20°C until use. Net peptide content (76%) rather than gross weight was used for dose calculations. During the studies, GLP-1 was given as an i.v. bolus injection of 4.5 pmol kg⁻¹ body wt followed by a continuous infusion of 1.5 pmol kg⁻¹ min⁻¹ for 60 min.

**Study protocol**

Rates of glucose appearance ($R_a$) and disappearance ($R_d$) were determined using infusion of 3-3H-glucose, which allowed evaluation of the effect of GLP-1 infusion on hepatic glucose production and peripheral glucose uptake. Each of the 13 subjects participated in two experiments, one with infusion of GLP-1 and one control experiment with saline infusion. Two different study series were performed; seven of the subjects received a somatostatin infusion during both the GLP-1 and the control experiment, and six subjects had the GLP-1 or control experiments without concomitant somatostatin infusion. GLP-1 and saline infusion studies were performed in random order, after an overnight fast, with at least 1 week in between visits. Two intravenous cannulas were inserted into forearm veins – in one arm for infusions and in the contralateral arm for sampling. The sampling catheter was kept patent with slow infusion of 0.9% saline.

After taking baseline samples at −15 and −5 min, a bolus dose of 25 μCi 3-3H-glucose (Amersham Life Science, Little Chalfont, Bucks, England) was injected intravenously at time 0, followed by a constant infusion of 0.25 μCi min⁻¹. The infusion continued until the end of the study after 180 min. Samples for analysis of plasma glucose, insulin, glucagon, GLP-1 and tritiated glucose were taken at 30, 60, 90, 100, 110 and 120 min.

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Without somatostatin (n = 6)</th>
<th>With somatostatin (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.8 ± 0.4</td>
<td>59.4 ± 0.3</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>64.6 ± 5.0</td>
<td>60.1 ± 4.7</td>
</tr>
<tr>
<td>Body mass index (kg m⁻²)</td>
<td>24.7 ± 3.4</td>
<td>23.0 ± 1.2</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol L⁻¹)</td>
<td>4.8 ± 0.5</td>
<td>4.2 ± 0.3</td>
</tr>
<tr>
<td>Fasting insulin (pmol L⁻¹)</td>
<td>54 ± 10</td>
<td>48 ± 6</td>
</tr>
<tr>
<td>2 h glucose (mmol L⁻¹)</td>
<td>6.4 ± 0.6</td>
<td>5.9 ± 1.7</td>
</tr>
<tr>
<td>Serum cholesterol (mmol L⁻¹)</td>
<td>6.91 ± 1.09</td>
<td>6.47 ± 1.07</td>
</tr>
<tr>
<td>Serum triglycerides (mmol L⁻¹)</td>
<td>1.05 ± 0.30</td>
<td>0.79 ± 0.22</td>
</tr>
</tbody>
</table>

*All values are mean ±SD.

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Table 1 Clinical characteristics of the subjects in the two studies with and without somatostatin infusion.
At 120 min, a bolus dose of GLP-1 was given (4.5 pmol kg\(^{-1}\)), followed by infusion of GLP-1 at a constant rate of 1.5 pmol kg\(^{-1}\) min\(^{-1}\) for 60 min. At time 180 min, all infusions were terminated. During the hour of GLP-1/saline infusion, samples were taken every 10 min.

The experimental series with somatostatin was performed as described above, with the addition of a somatostatin infusion. Concomitantly with the 3-\(^{3}H\) glucose infusion, an infusion of somatostatin (Ferring, Kiel, Germany) at a constant rate of 500 \(\mu\)g h\(^{-1}\) was started at time 0. Both of the infusions were given for over 10 min intervals during the 60 min of GLP-1/saline infusion. The metabolic clearance rate (MCR) of glucose was calculated as the \(R_d\) divided by the ambient plasma glucose concentration. The net effect of \(R_s\) and \(R_d\) on plasma glucose levels, i.e. the net glucose flow, was defined as the incremental difference in \(R_s\) and \(R_d\) over time, i.e. \(\Sigma (R_s - R_d)\). Thus, a positive net glucose flow (a positive value for \(R_s - R_d\)) indicates that glucose production is larger than glucose utilization, which increases plasma glucose. A negative net glucose flow (a negative value for \(R_s - R_d\)), on the other hand, means that glucose utilization exceeds glucose production, which results in a decreased plasma glucose.

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**RESULTS**

**Study without somatostatin**

After 120 min infusion of 3-\(^{3}H\)-glucose, GLP-1 or saline was added. The fasting or 120 min plasma glucose values did not differ between the two experimental series (fasting glucose 4.8 ± 0.2 in the GLP-1 study vs. 4.6 ± 0.1 mmol L\(^{-1}\) in the saline study, \(P = NS\); at 120 min, 4.8 ± 0.2 vs. 5.0 ± 0.2 mmol L\(^{-1}\), \(P = NS\); Fig. 1). The GLP-1 bolus and infusion reduced plasma glucose from 4.8 ± 0.2 at 120 min to 4.2 ± 0.3 mmol L\(^{-1}\) at 140 min (\(P = 0.007\)), whereas plasma glucose remained low until the end of the infusion at 180 min. In the saline experiment, plasma glucose did not differ between 120 and 180 min (\(P = NS\)). The decremental glucose area (AUC from baseline) from 120 to 180 min was numerically greater in the GLP-1 experiment than in the saline experiment (28.0 ± 6.2 vs. 7.9 ± 3.9 mmol L\(^{-1}\) min), although the difference was only marginally significant (\(P = 0.061\)).

The GLP-1 bolus and infusion at 120 min raised plasma GLP-1 levels from 3.3 ± 0.9 pmol L\(^{-1}\) at fasting to a peak level of 226.6 ± 33.7 pmol L\(^{-1}\) (\(P < 0.003\)) at 130 min (Fig. 2). GLP-1 levels then declined to 40.8 ± 16.4 pmol L\(^{-1}\) at 180 min. During the saline experiment, plasma GLP-1 levels were constantly low and not significantly different from baseline during the 180 min study.

Figure 3 shows that during the infusion of 3-\(^{3}H\)-glucose from 0 to 120 min, the serum insulin remained at fasting levels (GLP-1 56 ± 3 vs. saline 52 ± 5 pmol L\(^{-1}\), \(P = NS\)). The GLP-1 bolus and infusion at 120 min rapidly raised serum insulin to a peak value of 56 ± 3 pmol L\(^{-1}\) at 130 min (\(P = 0.003\)).
243 ± 67 pmol L\(^{-1}\) at 130 min (\(P = 0.032\)). At 150 min, serum insulin had returned to baseline levels in spite of the continuous GLP-1 administration (48 ± 4 pmol L\(^{-1}\), \(P = \text{NS vs.} \ 120\ \text{min}\)). During the saline infusion, insulin levels decreased slightly from 120 to 180 min (48 ± 4 vs. 43 ± 4 pmol L\(^{-1}\), \(P = 0.032\)). The incremental insulin area was significantly larger in the GLP-1 than in the saline experiment (2073 ± 705 vs. –168 ± 98 pmol L\(^{-1}\) \(\times\) min, \(P = 0.018\)).

After 120 min of tracer infusion, plasma glucagon (Fig. 4) did not differ between the two experimental series (40 ± 1 vs. 39 ± 2 ng L\(^{-1}\), \(P = \text{NS}\)). GLP-1 decreased glucagon levels at the end of the infusion to 32 ± 3 ng L\(^{-1}\) at 180 min (vs. saline 39 ± 2 ng L\(^{-1}\), \(P = 0.034\)). Although the decremental glucagon area during 120–180 min was numerically larger in the GLP-1 than in the saline experiment, the difference did not reach statistical significance (93 ± 81 vs. –41 ± 59 ng L\(^{-1}\) min\(^{-1}\), \(P = 0.14\)).

The insulin to glucagon ratio increased sharply and significantly after the GLP-1 bolus and infusion (Fig. 5), to a peak value at 130 min (\(P = 0.044\ vs.\ \text{saline}\)). Despite the ongoing GLP-1 infusion, the ratio of insulin to glucagon then returned to baseline levels at 150 min (\(P = \text{NS vs.} \ \text{saline}\)).

The rate of glucose appearance (\(R_a\)) and disappearance (\(R_d\)) between 120 and 180 min (Figs 6 and 7) did not differ significantly between GLP-1 and saline ex-
periments at any individual time point \((P = \text{NS})\). However, during GLP-1 infusion, the slope of the decrement of \(R_a\) from 130 to 150 min differed significantly from the baseline decrement \((P = 0.003)\), while during the saline infusion, the slope of \(R_a\) at 130–150 min did not differ from the baseline \((P = \text{NS})\). This shows that GLP-1 had reduced \(R_a\). Similarly, the \(R_d\) slope of decrement differed significantly between baseline and 130–150 min during the GLP-1 infusion \((P = 0.004)\), but not during the saline infusion \((P = \text{NS})\). Due to the more marked reduction in plasma glucose than in \(R_d\), the MCR of glucose was increased by GLP-1 (Fig. 8). Thus, the MCR curves in the two experimental series differed significantly from each other \((P = 0.024)\). Calculating the net glucose flow, i.e. the incremental difference between \(R_a\) and \(R_d\), gives the resultant effect of these two variables on the ambient plasma glucose level. Figure 9 shows the net glucose flow from 120 to 180 min. In the GLP-1 experiment, the net glucose flow decreased significantly between 120 and 180 min \((P = 0.012)\), which means that the \(R_a\) was reduced to a larger extent than \(R_d\), resulting in a decrease in plasma glucose. There was no significant difference in the net glucose flow from 120 to 180 min during the saline infusion \((P = \text{NS})\).

**Study with somatostatin**

The 2 h somatostatin infusion reduced the plasma glucose level during both GLP-1 \((4.5 \pm 0.2 \text{ mmol L}^{-1} \text{ at fasting vs. } 3.2 \pm 0.2 \text{ mmol L}^{-1} \text{ at 120 min, } P = 0.002)\) and saline experiments \((4.4 \pm 0.2 \text{ vs. } 3.4 \pm 0.3 \text{ mmol L}^{-1}, \text{ respectively})\).
From 120 to 180 min, plasma glucose increased slightly in both groups (GLP-1: to 3.4 ± 0.3 mmol L⁻¹, P = 0.049 vs. 120 min; saline: to 3.8 ± 0.4 mmol L⁻¹, P = 0.033 vs. 120 min). The increase in plasma glucose during this third hour did not differ in the GLP-1 and saline experiments (incremental glucose area 120–180 min: 6.43 ± 3.48 vs. 8.64 ± 5.30 mmol L⁻¹ · min⁻¹, P = NS).

The GLP-1 bolus and infusion at 120 min raised plasma GLP-1 levels from 6.5 ± 0.9 pmol L⁻¹ at fasting to a peak level of 273.3 ± 28.3 pmol L⁻¹ (P < 0.001) at 130 min (Fig. 2). Plasma GLP-1 levels then decreased to 44.1 ± 12.5 pmol L⁻¹ at 180 min. During the saline experiment, plasma GLP-1 levels were constantly low during the 180 min study.

Serum insulin (Fig. 3) was significantly reduced during the somatostatin infusion from 0 to 30 min in both GLP-1 (51 ± 4 at fasting vs. 22 ± 1 pmol L⁻¹ at 30 min, P < 0.001) and saline experiments (45 ± 4 vs. 26 ± 4 pmol L⁻¹, P = 0.003). During the saline experiment, serum insulin remained low for the rest of the study. In the GLP-1 experiment, serum insulin remained low until 120 min. After the start of GLP-1 infusion, there was a transient increase in serum insulin to 29 ± 5 pmol L⁻¹ at 130 min (P = 0.05 vs. saline). At 140 min, serum insulin had again returned to baseline levels.

The somatostatin infusion also decreased plasma glucagon levels (Fig. 4) from 0 to 30 min during both GLP-1 (49 ± 2 at fasting vs. 30 ± 2 ng L⁻¹ at 30 min, P < 0.001) and saline experiments (45 ± 4 vs. 29 ± 2 ng L⁻¹, P = 0.003). During the saline experiment, serum glucagon remained low for the rest of the study. In the GLP-1 experiment, serum glucagon remained low until 120 min. After the start of GLP-1 infusion, serum glucagon increased to 30 ± 3 ng L⁻¹ at 130 min (P = 0.05 vs. saline). After the somatostatin infusion, serum glucagon had again returned to baseline levels.
and saline experiments (49 ± 2 vs. 30 ± 2 ng L⁻¹, \( P < 0.001 \)). Plasma glucagon then remained unchanged during the rest of both GLP-1 and saline experiments.

Despite the increase in insulin at 130 min during the GLP-1 infusion, the insulin to glucagon ratio (Fig. 5) did not differ significantly between GLP-1 and saline, although at 130 min, the ratio was numerically larger in the GLP-1 experiment (\( P = 0.083 \)).

Figures 6 and 7 show the rate of glucose appearance (\( R_a \)) and disappearance (\( R_d \)) between 120 and 180 min. \( R_a \) and \( R_d \) did not differ between GLP-1 and saline experiments (\( P = NS \)). Neither was there a difference in the MCR of glucose (Fig. 8) between GLP-1 and saline (\( P = NS \)). Figure 9 shows that the infusion of GLP-1 did not alter the net glucose flow during the somatostatin experiments, since the increase in net glucose flow from 120 to 180 min was similar in GLP-1 and saline infusion (\( P = NS \)).

**DISCUSSION**

It is well known that GLP-1 reduces circulating glucose levels in humans (Nauck et al. 1993b, Hvidberg et al. 1994, Ritzel et al. 1995, Willms et al. 1996). This study was aimed at determining whether the effects of GLP-1
on glucose turnover are due to effects on liver glucose output and/or to effects on peripheral glucose uptake, and whether the effects are direct effects of GLP-1 or indirect effects, due to GLP-1-induced changes in insulin and glucagon levels. We found that infusion of GLP-1 alone reduced plasma glucose and the rate of appearance of glucose, while the metabolic clearance rate of glucose was increased. Simultaneously, the insulin to glucagon ratio increased. When somatostatin was concomitantly infused, the GLP-1-induced changes in insulin and glucagon were largely abolished. Plasma glucose was then unaffected by GLP-1 infusion, as was the rate of glucose appearance and disappearance and the metabolic clearance rate of glucose. The results suggest that the effects of GLP-1 on glucose turnover are mediated through changes in insulin and glucagon levels and not by direct effects of the peptide per se.

As in a previous study by Hvidberg et al. (1994), we found that GLP-1, in the absence of somatostatin, reduced the rate of glucose appearance and increased the metabolic clearance rate of glucose. However, we also found a decrease in the glucose rate of disappearance during the GLP-1 infusion, which was not noted in the previous study. This could tentatively be explained by the decreased plasma glucose levels during the GLP-1 infusion in these fasting subjects. The decrease in $R_d$ is contrary to suggestions that GLP-1 could increase the peripheral insulin sensitivity, which would increase glucose $R_o$. Thus, our present finding agrees with two recent reports suggesting that GLP-1 does not directly affect glucose elimination in healthy subjects as judged by the disappearance of glucose after an intravenous glucose bolus during infusion of somatostatin (Toft-Nielsen et al. 1996) or as judged by the insulin sensitivity calculated from results of a hyperinsulinaemic, euglycaemic clamp (Orskov et al. 1996).

In spite of the finding that $R_a$ and $R_d$ seemed to be simultaneously reduced by GLP-1 (see Figs 4, 6 and 7), there was a marked change in the net glucose flow, i.e. the net effect of glucose production by the liver vs. glucose uptake in the periphery. Thus, GLP-1 induced a slight delay in the reduction of $R_d$ compared to the reduction of $R_a$, which resulted in a negative net glucose flow, causing a decrease in the plasma glucose level. At the same time, the metabolic clearance rate of glucose was increased, since the $R_d$ was not reduced with a similar magnitude as the plasma glucose level. The increase in the glucose metabolic clearance rate could be interpreted as an effect of the increased serum insulin level, which stimulated glucose clearance.

GLP-1 is well known to reduce plasma glucagon levels both in healthy subjects and in subjects with diabetes (Gutniak et al. 1992, Nauck et al. 1993a, b, Ritzel et al. 1995). However, we could not demonstrate an immediate effect on plasma glucagon levels in our study during the GLP-1 infusion in the absence of somatostatin, in spite of the fact that GLP-1 levels were increased to supraphysiological levels. We interpret this to be a consequence of the decreased plasma glucose level in these fasting individuals, causing a counter-regulatory stimulation of glucagon secretion. This is supported by the finding that, when the glucose level increased slightly at the end of the GLP-1 infusion, there was a significant reduction in the plasma glucagon levels. Similar to these findings, a recent study in fasted rats showed that GLP-1 infusion increased instead of decreased glucagon levels, interpreted as a counter-regulatory effect of the decreased plasma glucose levels (van Dijk et al. 1996). Nevertheless, even though there...
was no decrease in plasma glucagon during the first 30 min following the GLP-1 infusion, there was a reduction of hepatic glucose production. At the same time, the ratio of insulin to glucagon was significantly increased more than sevenfold by the GLP-1 infusion. This would suggest that the insulin to glucagon ratio is an important factor governing hepatic glucose production. Glucagon has previously been considered the most important regulator of hepatic glucose production in vivo (Cherrington et al. 1987). However, a more recent study indicates that insulin is also a potent regulator of glucose production, on a molar basis more potent than glucagon (Steiner et al. 1990). Thus, the increase in insulin caused by the GLP-1 infusion would be sufficient to reduce hepatic glucose production, although there was no decrease in plasma glucagon levels.

During the infusion of somatostatin, the circulating insulin levels were significantly reduced, as expected with the rather large dose of somatostatin employed. Still, in spite of the ongoing somatostatin infusion, GLP-1 increased insulin levels above basal. This indicates that GLP-1 is a very powerful insulinotropic agent, in line with other findings that GLP-1 infusion can overcome very high somatostatin concentrations (Toft-Nielsen et al. 1996). In fact, a somatostatin infusion rate twice that of ours (i.e. 1000 μg h⁻¹) was needed to totally block the insulin-releasing effect of GLP-1 (Toft-Nielsen et al. 1996). However, the increase in insulin induced by GLP-1 was notably reduced by somatostatin, which indicates that somatostatin inhibits the insulinotropic effect of GLP-1. Similarly, glucagon levels were markedly reduced by the somatostatin infusion, and therefore GLP-1 could not reduce the low glucagon levels further. Also, the increase in the insulin to glucagon ratio observed in the study with GLP-1 alone was abolished in the experiment with somatostatin.

A main finding in this study is that GLP-1 failed to reduce $R_g$ in the presence of somatostatin. Several explanations might be offered for this finding. First, somatostatin could by itself inhibit the effects of GLP-1 on hepatic glucose production. This, however, is opposed by the fact that somatostatin could not fully inhibit the insulinotropic effect of GLP-1. A second and more likely explanation is that GLP-1 does not have any direct effects on the liver, but reduces $R_g$ through its impact on insulin and glucagon levels. This explanation is also supported by recent studies showing that GLP-1 does not affect the disappearance of glucose after in intravenous glucose bolus during infusion of somatostatin (Toft-Nielsen et al. 1996) or the glucose infusion rate required to maintain euglycaemia in a hyperinsulinaemic, euglycaemic clamp (Orskov et al. 1996). Also, in accordance with this hypothesis, the insulin to glucagon ratio was not significantly increased by GLP-1 during the somatostatin infusion in our present study. The slight increase in insulin was probably too small to affect the hepatic glucose production, especially since the insulin to glucagon ratio was not changed. Thus, it seems that GLP-1 does not reduce the rate of glucose appearance by direct effects on gluconeogenesis and glycogenolysis in the liver. This is supported by several reports that GLP-1 receptors can not be demonstrated on rat hepatocytes (Blackmore et al. 1991, Orskov & Poulsen 1991, Fehmann et al. 1995). However, other studies have reported GLP-1 binding to rat hepatocytes (Villanueva et al. 1995) and also GLP-1 receptor mRNA to be present in rat (Egan et al. 1994) and mouse liver (Campos et al. 1994). Furthermore, GLP-1 has been demonstrated to have glycolytic effects on isolated rat hepatocytes (Valverde et al. 1994). Therefore, more studies on the possible direct effects of GLP-1 on hepatocytes are needed. It is currently not known whether human hepatocytes express GLP-1 receptors.

In summary, we have demonstrated that GLP-1 inhibits hepatic glucose production and increases the metabolic clearance rate of glucose in humans, which results in a reduction of plasma glucose. Furthermore, somatostatin abolishes the effects of GLP-1 on glucose turnover, leaving plasma glucose levels unaffected. Finally, the GLP-1-induced changes of insulin and glucagon secretion are eliminated by somatostatin infusion. We conclude that the effects of GLP-1 on glucose turnover are indirectly mediated by changes in insulin and glucagon secretion, rather than direct effects of the peptide per se.

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GLP-1 and hepatic glucose production · H Larsson et al.


