Effects of intraportal exenatide on hepatic glucose metabolism in the conscious dog

Dale S. Edgerton, Zhibo An, Kathryn M. S. Johnson, Tiffany Farmer, Ben Farmer, Doss Neal, and Alan D. Cherrington

Department of Molecular Physiology and Biophysics, Vanderbilt University Medical Center, Nashville, Tennessee

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Edgerton DS, An Z, Johnson KM, Farmer T, Farmer B, Neal D, Cherrington AD. Effects of intraportal exenatide on hepatic glucose metabolism in the conscious dog. Am J Physiol Endocrinol Metab 305: E132–E139, 2013. First published May 14, 2013; doi:10.1152/ajpendo.00160.2013.—Incretins improve glucose metabolism through multiple mechanisms. It remains unclear whether direct hepatic effects are an important part of exenatide’s (Ex-4) acute action. Therefore, the objective of this study was to determine the effect of intraportal delivery of Ex-4 on hepatic glucose production and uptake. Fasted conscious dogs were studied during a hyperglycemic clamp in which glucose was infused into the hepatic portal vein. At the same time, portal saline (control; n = 8) or exenatide was infused at low (0.3 pmol·kg⁻¹·min⁻¹, Ex-4-low; n = 5) or high (0.9 pmol·kg⁻¹·min⁻¹, Ex-4-high; n = 8) rates. Arterial plasma glucose levels were maintained at 160 mg/dl during the experimental period. This required a greater rate of glucose infusion in the Ex-4-high group (1.5 ± 0.4, 2.0 ± 0.7, and 3.7 ± 0.7 mg·kg⁻¹·min⁻¹ between 30 and 240 min in the control, Ex-4-low, and Ex-4-high groups, respectively). Plasma insulin levels were elevated by Ex-4 (arterial: 4,745 ± 428, 5,710 ± 355, and 7,262 ± 1,053 μU/ml; hepatic sinusoidal: 14,679 ± 355, 15,341 ± 2,208, and 20,445 ± 4,020 μU/ml, 240 min, area under the curve), whereas the suppression of glucagon was nearly maximal in all groups. Although glucose utilization was greater during Ex-4 infusion (5.92 ± 0.53, 6.41 ± 0.57, and 8.12 ± 0.54 mg·kg⁻¹·min⁻¹), when indices of hepatic, muscle, and whole body glucose uptake were expressed relative to circulating insulin concentrations, there was no indication of insulin-independent effects of Ex-4. Thus, this study does not support the notion that Ex-4 generates acute changes in hepatic glucose metabolism through direct effects on the liver.

exenatide; exendin-4; incretin; hepatic glucose metabolism; hepatic glucose uptake; hepatic glycogen accumulation in rat hepatocytes, an effect associated with increased and decreased glycogen synthase and phosphorylase activities, respectively (3, 45, 54), although others were unable to reproduce those results (47). In vivo, in response to physiological GLP-1 infusion in humans and dogs, some studies have identified insulin-independent increases in glucose uptake, including by the liver (11, 12, 22, 48), whereas others have not (50, 57). Even at pharmacological levels, the results are mixed (2, 13, 23, 48, 59, 60). Thus, considerable controversy exists regarding the direct effects of incretin hormones on the liver.

The purpose of the present study was to further explore the effect of Ex-4 on the stimulation of net hepatic glucose uptake and inhibition of endogenous glucose production using the conscious dog. In an attempt to expose a direct effect of Ex-4 on the liver, Ex-4 was infused into the hepatic portal vein, thereby bringing about a high concentration at the liver while at the same time minimizing exposure of other tissues, including the pancreas, to Ex-4.

RESEARCH DESIGN AND METHODS

Animals and surgical procedures. Experiments were conducted on twenty-one 42-h-fasted conscious mongrel dogs of either sex (18–25 kg). This length of fast does not induce hypoglycemia, raise the plasma levels of stress hormones, or exhaust liver glycogen in the dog (42, 43). Housing and diet have been described previously (21). The surgical facility met the standards published by the American Association for the Accreditation of Laboratory Animal Care, and the protocols were approved by the Vanderbilt University Medical Center Institutional Animal Care and Use Committee. All dogs underwent a laparotomy 2 wk before the experiment to implant portal vein infusion catheters into the jejunal and splenic veins, sampling catheters into the femoral artery and the iliac, portal, and hepatic veins, and ultrasonic flow probes around the hepatic artery and the iliac and portal veins, as described elsewhere (21). Each dog was used for only one experiment. All dogs were healthy as indicated by 1) leukocyte count <18,000/mm³, 2) a hematocrit >35%, 3) a good appetite, and 4) normal stools.

Address for reprint requests and other correspondence: D. S. Edgerton, Molecular Physiology and Biophysics, Vanderbilt University Medical Center, 710 Robinson Research Bldg., Nashville, TN 37232-0615 (e-mail: dale.edgerton@vanderbilt.edu).
Net hepatic balance (NHB) was calculated using the arteriovenous difference method according to the formula: $\text{NHB} = \text{Load}_{\text{out}} - \text{Load}_{\text{in}}$, where $\text{Load}_{\text{out}} = [H] \times \text{HF}$ and $\text{Load}_{\text{in}} = [A] \times \text{AF} + [P] \times \text{PF}$ and where $[H]$, $[A]$, and $[P]$ are arterial and portal vein hormone concentrations, respectively, and $\text{AF}$ and $\text{PF}$ are the respective percent contributions of arterial and portal flow to total hepatic blood flow. Ex-4 plasma clearance was determined by dividing the Ex-4 infusion rate by its arterial concentration. Tracer-determined whole body glucose appearance and utilization were measured using a primed, constant infusion of $[3^{-3}H]$glucose. Glucose turnover was calculated using a two-compartment model (38) with canine parameters (16).

**Statistical analysis.** The data were analyzed for differences from the basal period and from the control group. Statistical comparisons were carried out using two-way repeated-measures ANOVA (SigmaStat; SPSS). One-way ANOVA comparison tests were used post hoc when significant $F$ ratios were obtained. Significance was established when $P < 0.05$ (2-sided test).

**RESULTS**

Intraportal Ex-4 infusion resulted in steady-state levels of $68 \pm 10$ and $76 \pm 10$ pmol/l in arterial and portal plasma, respectively, in the Ex-4-low group (last 3 h; Fig. 1). In the Ex-4-high group, the arterial and portal plasma Ex-4 levels were $211 \pm 20$ and $283 \pm 19$ pmol/l, respectively. Arterial Ex-4 clearance was $5 \pm 1$ ml·kg$^{-1}$·min$^{-1}$ in both groups (data not shown).

Portal and peripheral vein glucose infusions were used to increase the circulating arterial plasma glucose levels to $\sim 160$ mg/dl during the experimental period in each group (Fig. 2). This resulted in similar increases in hepatic glucose load between groups (Fig. 2). The peripheral glucose infusion rate required to maintain the same level of hyperglycemia was dose-dependently increased by Ex-4 ($1.5 \pm 0.4$, $2.0 \pm 0.7$, and $3.7 \pm 0.7$ mg·kg$^{-1}$·min$^{-1}$ between 30 and 240 min in the control, Ex-4-low, and Ex-4-high groups, respectively; $P < 0.05$, Ex-4-high vs. control; Fig. 2).
In response to circulating hyperglycemia, the plasma insulin levels (µU/ml) in the control group increased from 7 ± 1 to 21 ± 2 in the artery (Δ of +14) and from 18 ± 3 to 64 ± 7 in the liver sinusoids (Δ of +46; Fig. 3). Arterial and hepatic insulin levels increased to a greater extent in the presence of Ex-4 in the Ex-4-low group from 5 ± 1 to 25 ± 2 (Δ of +20; arterial) and from 11 ± 2 to 67 ± 10 (Δ of +56; hepatic sinusoidal) and in the Ex-4-high group from 6 ± 1 to 32 ± 5 (Δ of +26; arterial, P < 0.05 vs. control) and from 15 ± 2 to 94 ± 22 (Δ of +79; hepatic sinusoidal) (Fig. 3). Arterial and hepatic sinusoidal glucagon levels declined similarly in each group (Fig. 3). Arterial cortisol, epinephrine, and norepinephrine levels remained basal and unchanged throughout each study (data not shown).

 Increased liver glucose and insulin levels resulted in a switch in net hepatic glucose balance from output to uptake during the basal and experimental periods, respectively. Net hepatic glucose balance (mg·kg⁻¹·min⁻¹) switched from 1.84 ± 0.25 to −2.01 ± 0.41 (Δ of −3.85) in the control group, from 1.82 ± 0.22 to −2.06 ± 0.32 (Δ of −3.88) in the Ex-4-low group, and from 1.55 ± 0.18 to −3.21 ± 0.66 (Δ of −4.76) in the Ex-4-high group (Fig. 4). During the last hour of the study, net hepatic fractional glucose extraction rates were 6.7 ± 1.1, 7.0 ± 0.8, and 10.0 ± 1.7% in the control, Ex-4-low, and Ex-4-high groups, respectively. Endogenous glucose production was suppressed similarly during the hyperglycemic hyperinsulinemic clamp from 2.43 ± 0.12 to 0.92 ± 0.16 (Δ of −1.51), 2.27 ± 0.12 to 0.54 ± 0.11 (Δ of −1.73), and 2.38 ± 0.13 to 0.88 ± 0.25 (Δ of −1.50) mg·kg⁻¹·min⁻¹ in the control, Ex-4-low, and Ex-4-high groups, respectively, during the basal and experimental periods (Fig. 4).

Glucose utilization increased during the experimental period. Net hindlimb glucose uptake increased from 4.08 ± 0.87

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**Fig. 3.** Arterial and hepatic sinusoidal plasma insulin and glucagon levels in conscious dogs during the basal (−40 to 0 min) and experimental periods (0–240 min) in control, Ex low, or Ex high Ex-4-treated animals (means ± SE; *P < 0.05 vs. control, 2-way repeated-measures ANOVA followed by the Student-Newman-Keuls post hoc test).

**Fig. 4.** Net hepatic glucose balance and tracer-determined endogenous glucose production in conscious dogs during the basal (−40 to 0 min) and experimental periods (0–240 min) in control, Ex low, or Ex high Ex-4-treated animals (means ± SE).

**Fig. 5.** Net hindlimb glucose uptake, tracer-determined whole body glucose utilization, and nonhepatic glucose uptake in conscious dogs during the basal (−40 to 0 min) and experimental periods (0–240 min) in control, Ex low, or Ex high Ex-4-treated animals (means ± SE; *P < 0.05 vs. control, 2-way repeated-measures ANOVA followed by the Student-Newman-Keuls post hoc test).
to 6.97 ± 1.37 (Δ of +2.89) mg/min in the control group, from 3.47 ± 0.69 to 8.89 ± 2.07 (Δ of +5.42) mg/min in the Ex-4-low group, and from 5.36 ± 0.94 to 10.69 ± 2.03 (Δ of +5.33) mg/min in the Ex-4-high group during the basal and experimental periods, respectively (Fig. 5). Tracer-determined whole body glucose utilization increased from 2.46 ± 0.10 to 5.92 ± 0.53 (Δ of +3.46), 2.27 ± 0.10 to 6.41 ± 0.57 (Δ of +4.14), and 2.42 ± 0.12 to 8.12 ± 0.54 (Δ of +5.70) mg·kg⁻¹·min⁻¹ in the control, Ex-4-low, and Ex-4-high groups, respectively, during the basal and experimental periods (P < 0.05 Ex-4-high vs. control; Fig. 5). Nonhepatic glucose uptake increased from 1.84 ± 0.25 to 2.94 ± 0.60 (Δ of +1.10), 1.82 ± 0.22 to 3.63 ± 0.80 (Δ of +1.81), and 1.55 ± 0.18 to 4.19 ± 1.10 (Δ of +2.64) mg·kg⁻¹·min⁻¹ in the control, Ex-4-low, and Ex-4-high dose groups, respectively (Fig. 5).

Although hepatic and nonhepatic glucose uptake tended to be increased by Ex-4, there were no insulin-independent effects since plasma insulin levels were also elevated dose dependently during hyperglycemia. When the areas under the curve of hepatic, nonhepatic, hindlimb, or whole body glucose uptake were divided by the areas under the curve of plasma insulin, there were no differences between groups in the resulting ratios (Fig. 6).

There was a switch from net hepatic lactate uptake to output and elevations in arterial lactate levels in all groups (Fig. 7), with the greatest change in these parameters occurring in the Ex-4-high group, consistent with increased liver glucose production and uptake directly by the liver’s exposure to insulin, glucagon, the glucose load, and the glucose gradient between the hepatic portal vein and arterial blood supply (8, 41). We observed that whereas glucagon levels, hepatic glucose load, and the portal vein/arterial glucose gradient were similar between groups during intraportal Ex-4 infusion, plasma insulin concentrations were elevated dose dependently by the treatment. Although hepatic glucose production was suppressed similarly between groups, net hepatic and whole body glucose uptake increased most with the highest dose of Ex-4. Previous studies have demonstrated a linearity of effect of arterial insulin on glucose utilization (between 13 and 120 μU/ml) (39) and of hepatic insulin on net hepatic glucose uptake (between 50 and 170 μU/ml) (46). Thus, when hepatic and nonhepatic glucose flux rates were expressed relative to the

**DISCUSSION**

The aim of this study was to determine the effect of Ex-4 on glucose metabolism during mild hyperglycemia induced by portal vein glucose infusion. Ex-4 was infused intraportally to maximize exposure at the liver while minimizing effects in nonhepatic tissues such as the pancreas. Hepatic glucose production and uptake are regulated directly by the liver’s exposure to insulin, glucagon, the glucose load, and the glucose gradient between the hepatic portal vein and arterial blood supply (8, 41). We observed that whereas glucagon levels, hepatic glucose load, and the portal vein/arterial glucose gradient were similar between groups during intraportal Ex-4 infusion, plasma insulin concentrations were elevated dose dependently by the treatment. Although hepatic glucose production was suppressed similarly between groups, net hepatic and whole body glucose uptake increased most with the highest dose of Ex-4. Previous studies have demonstrated a linearity of effect of arterial insulin on glucose utilization (between 13 and 120 μU/ml) (39) and of hepatic insulin on net hepatic glucose uptake (between 50 and 170 μU/ml) (46). Thus, when hepatic and nonhepatic glucose flux rates were expressed relative to the
increases in plasma insulin concentrations, no insulin-independent effects of Ex-4 were apparent.

Previous studies have suggested that GLP-1 and Ex-4 can affect glucose metabolism by multiple mechanisms (37). Most importantly, incretins are known to stimulate insulin secretion during hyperglycemia. In addition, glucagon secretion may be reduced, and some studies have suggested that incretins may have direct effects on tissues such as the liver, increasing insulin sensitivity (1, 10, 26) and modifying molecular regulators of hepatic glucose metabolism (3, 14, 15, 45, 54), thereby modifying liver glucose production and uptake independently from the effects of changes in insulin secretion. On the other hand, other studies have not observed a direct effect (1, 10, 26), and our data support the latter conclusion. It should be noted that whereas Ex-4 infused at 0.3 pmol·kg⁻¹·min⁻¹ produced a rise in Ex-4 that was within the clinical range (a rise of 50–75 pmol/l is typical following a 10-µg exenatide injection in humans), delivery of Ex-4 at 0.9 pmol·kg⁻¹·min⁻¹ resulted in levels that were above the therapeutic range (34). Thus, although it is possible that even higher doses of Ex-4 might produce insulin-independent effects, those results would be less clinically relevant, at least insofar as hepatic sensitivity to Ex-4 is similar in the human and the dog.

The portal vein is richly innervated, and GLP-1 receptors are expressed on nerve terminals in the region (58). In addition, the portal vein can sense changes in glucose concentrations (41), and this signal may interact with signals generated by the GLP-1 receptor to potentiate hepatic glucose uptake (5, 58). Therefore, simultaneous intraportal Ex-4/glucose infusion might be more likely to produce a direct hepatic effect. Whereas some studies have suggested that elevations in both portal vein glucose and GLP-1 are important for hepatic (31) and nonhepatic (32, 33) insulin-independent effects of GLP-1, in other studies the route of GLP-1 infusion (portal vs. peripheral) did not modify the hepatic response to intraportal glucose (12, 13). In any case, even though both glucose and Ex-4 were infused into the portal vein in the present study, no insulin-independent effects were observed.

Although Ex-4 has been shown to have a higher potency than GLP-1 for acute glucose-lowering effects (66), this is likely to be due at least partly to rapid degradation of GLP-1 [Ex-4 vs. GLP-1 clearance was 5 vs. 38 ml·kg⁻¹·min⁻¹ (22)]. In previous studies in the dog (12, 22), when GLP-1 was infused to maintain a constant circulating level within the physiological range (i.e., increases of 25–50 pM), insulin-independent stimulation of net hepatic glucose uptake was observed (although it was small). In addition, net hepatic glucose uptake responded dose-dependently to supraphysiological hepatic GLP-1 concentrations up to 200 pmol/l (12). On the other hand, there were no insulin-independent effects of Ex-4 in the present study at portal vein concentrations of 76 or 283 pmol/l. This suggests that Ex-4 does not have the same potency as GLP-1, at least in regard to direct hepatic effects in normal healthy dogs. These findings support the notion that GLP-1 and Ex-4 may act via distinct receptor isoforms and/or postreceptor signal transduction pathways (49).

In another study in dogs, net hepatic glucose uptake was increased marginally by Ex-4 under hyperglycemic hyperinsulinemic conditions during a somatostatin clamp (67). A possi-

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Table 1. Arterial blood glycerol levels, net hepatic balance, and plasma free fatty acid levels

<table>
<thead>
<tr>
<th>Group</th>
<th>Basal Period, min</th>
<th>Experimental Period, min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Arterial blood glycerol, µmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>101 ± 14</td>
<td>73 ± 10</td>
</tr>
<tr>
<td>Low</td>
<td>95 ± 14</td>
<td>82 ± 12</td>
</tr>
<tr>
<td>High</td>
<td>84 ± 7</td>
<td>72 ± 8</td>
</tr>
<tr>
<td>Net hepatic glycerol uptake, µmol·kg⁻¹·min⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.8 ± 0.2</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>Low</td>
<td>1.4 ± 0.7</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>High</td>
<td>1.9 ± 0.1</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>Arterial plasma free fatty acids, µmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2,025 ± 120</td>
<td>903 ± 140</td>
</tr>
<tr>
<td>Low</td>
<td>1,025 ± 120</td>
<td>903 ± 140</td>
</tr>
<tr>
<td>High</td>
<td>982 ± 58</td>
<td>866 ± 61</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. control, 2-way repeated-measures ANOVA followed by Student-Newman-Keuls post hoc test.

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ble explanation for the discrepancy between that study and the present study is that in the former study insulin was infused into a peripheral vein during somatostatin infusion. When insulin is secreted or infused into the portal vein, as occurred in the present study, insulin concentrations are consistently threefold higher in the portal vs. arterial blood supply (28, 44). In contrast, when insulin is infused into a peripheral vein, portal levels are slightly lower than arterial levels (53). Thus, although arterial insulin levels increased from basal almost fivefold during the clamp in the study by Zheng et al. (67), portal vein insulin concentrations would have increased less than twofold. Therefore, it is possible that Ex-4 may potentiate the effects of insulin action on liver glucose uptake during a smaller rise in hepatic insulin levels, whereas the physiological liver insulin levels generated by mild hyperglycemia in the present study may have been saturating in regard to an insulin-Ex-4 interaction. In the aforementioned study, Ex-4 was administered by subcutaneous injection (20 μg), whereas in the present study, constant intraportal infusion was used (20 μg over 240 min at the higher dose). Since Ex-4 levels were not measured in the previous study, it is difficult to know how circulating levels may have compared, but extrapolation from the kinetics of intravenous vs. subcutaneous Ex-4 administration in the rat (51) suggests that peak Ex-4 levels may have been lower in the present study. Finally, the previous (67) and present studies were carried out following different lengths of fast (18 vs. 42 h). Like the human, after several days of fasting the dog maintains significant hepatic glycogen stores, and glycogenolysis remains a major contributor to hepatic glucose production (42, 43, 53). In addition, other studies have observed GLP-1-mediated insulin-independent increases in hepatic glucose uptake in 42-h-fasted dogs (13, 48). Thus, length of the fast is not likely to have been a contributing factor.

Other studies have suggested that Ex-4 and GLP-1 can create molecular changes that could directly affect glucose metabolism. For example, when rat models of insulin resistance and diabetes were treated with Ex-4 at 1.7 pmol·kg⁻¹·min⁻¹ for 3 days, there were effects on liver, skeletal muscle, and adipose tissues, including improvements in glucose transporter expression and glucose transport associated with normalization of phosphoinositide 3-kinase (PI3K) activity (45). In other studies, when tissues from normal rats were incubated with Ex-4, skeletal muscle glucose utilization and oxidation increased, as did glycogen synthase activity and glycogen content in isolated hepatocytes (3), effects associated with activation of PI3K, PKC, and protein phosphatase-1 (54). In addition, glucokinase activity was increased in hepatocytes from db/db, high-fat-fed, and streptozotocin- and alloxan-treated mice that had been pretreated with Ex-4, although there was no effect in lean mice (14, 15). Although these studies suggest the potential for direct incretin effects in liver, muscle, and adipose tissues, differences in species, dose, period of treatment, and state of metabolic derangement may explain why we and others have not observed direct effects of Ex-4 on glucose metabolism.

GLP-1 infusion has been shown clinically to reduce hepatic glucose production in type 2 diabetic patients in part through inhibition of glucagon secretion (9, 25). In the present study, glucagon levels were reduced similarly in the presence of hyperglycemia and hyperinsulinemia in all groups, indicating that there was no effect of Ex-4. It should be noted, however, that a highly specific glucagon assay does not exist, hampering accurate measurement of glucagon suppression (18, 27). In fact, the majority of what was measured during the experimental period of the present study was probably cross-reacting material, not glucagon (20). Thus, since glucagon secretion was already close to maximally suppressed by the experimental conditions, an effect of Ex-4 could not become apparent. Incretin-mediated suppression of glucagon may play a greater role under circumstances in which glucagon levels are appropriately elevated, such as what occurs in diabetes.

In summary, this study demonstrates that Ex-4 can indirectly increase hepatic glucose uptake through the stimulation of insulin secretion, but it does not support the premise that Ex-4 can generate acute changes in hepatic glucose metabolism through direct effects on the liver.

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Present address of K. M. S. Johnson: Department of Biology, Beloit College, Beloit, WI.

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DISCLOSURES

Amylin provided financial support and exendatide to complete the reported studies. A. D. Cherrington is a consultant to Amylin. There are no other conflicts of interest to declare. D. S. Edgerton is the guarantor of this work, had full access to all of the data, and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

AUTHOR CONTRIBUTIONS

D.S.E. and A.D.C. contributed to the conception and design of the research; D.S.E., Z.A., K.M.J., T.F., B.F., and D.N. performed the experiments; D.S.E. and A.D.C. analyzed the data; D.S.E. and A.D.C. interpreted the results of the experiments; D.S.E. prepared the figures; and D.S.E. and A.D.C. drafted the manuscript; D.S.E. and A.D.C. edited and revised the manuscript; D.S.E., Z.A., K.M.J., T.F., B.F., D.N., and A.D.C. approved the final version of the manuscript.

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