Intraportally delivered GLP-1, in the presence of hyperglycemia induced via peripheral glucose infusion, does not change whole body glucose utilization.

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Am J Physiol Endocrinol Metab 294: E380–E384, 2008. First published December 4, 2007; doi:10.1152/ajpendo.00642.2007.—After a meal, glucagon-like peptide-1 (GLP-1) and glucose levels are significantly greater in the hepatic portal vein than in the artery. We have previously reported that, in the presence of intraportal glucose delivery, a physiological increase of GLP-1 in the hepatic portal vein increases nonhepatic glucose uptake via a mechanism independent of changes in pancreatic hormone secretion. The aim of the present study was to determine whether intraportal glucose delivery is required to observe this effect.

Experiments consisted of a 40-min basal period, followed by a 240-min experimental period, during which conscious 42-h fasted animals were shown to be in good health, as previously described (11). During the previous study, the presence of GLP-1 did not alter pancreatic hormone levels; however, in the present study, intraportal GLP-1 infusion did not result in an increase in whole body glucose utilization. This is despite the fact that arterial and hepatic portal vein GLP-1 levels were maintained at the same level as the previous study. Therefore, a physiological elevation of GLP-1 in the hepatic portal vein does not increase whole body glucose uptake when hyperglycemia is induced by peripheral glucose infusion. This indicates that a physiological increase in GLP-1 augments glucose utilization only when GLP-1 and glucose gradients conditions mimic the postprandial state.

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Plasma glucose and glucagon-like peptide-1 (GLP-1) levels were determined in dogs after an intraportal infusion of either GLP-1 or saline (Sal). Levels were initially (−40 to 0 min), but both arterial and portal levels increased significantly (P < 0.05) during the experimental period (0 to 240 min) in response to the glucose clamp. There were no significant differences between groups in either the basal or experimental period.

Plasma insulin and glucagon levels. The arterial and hepatic portal vein plasma insulin levels were similar between groups during the basal period (Fig. 3A). Both groups exhibited similar increases in response to peripheral glucose infusion (to 24 ± 1 and 28 ± 5 µU/ml in arterial plasma, and to 81 ± 12 and 86 ± 10 µU/ml in hepatic portal vein plasma in the Sal and GLP-1 groups, respectively) (Fig. 3A). The sinusoidal plasma glucagon levels were similar between groups during the basal period (Fig. 3B) and decreased in a similar manner (to 22 ± 5 and 22 ± 5 pg/ml, Sal and GLP-1, respectively) during the experimental period.

Hepatic blood flow, NHGB, and non-HGU. Hepatic arterial blood flow during the basal period and the experimental period were similar between groups, as were the hepatic portal vein blood flows. In the basal state, net hepatic glucose output was

**RESULTS**

Plasma glucose levels. Plasma glucose levels in the artery (159 ± 1 and 162 ± 1 mg/dl) and hepatic portal vein (159 ± 1 and 162 ± 1 mg/dl) in the Sal and GLP-1 groups, respectively, were increased similarly in response to peripheral glucose infusion (Fig. 1A).

Plasma GLP-1 levels. There was no difference between groups in basal GLP-1 levels in either arterial or hepatic portal vein plasma (Fig. 1B), nor did the levels change in response to saline infusion. On the other hand, they rose in both the artery (29.4 ± 1.5 pmol/l) and hepatic portal vein (57.7 ± 4.5 pmol/l) in response to intraportal GLP-1 infusion (Fig. 1B).

GIR. There was no difference in the GIRs, required to maintain the glucose clamp, between the two groups (6.1 ± 1.0 vs. 6.4 ± 1.2 mg·kg⁻¹·min⁻¹, average over final 2 h, Sal vs. GLP-1) (Fig. 2).

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Hepatic blood flow, NHGB, and non-HGU. Hepatic arterial blood flow during the basal period and the experimental period were similar between groups, as were the hepatic portal vein blood flows. In the basal state, net hepatic glucose output was...
similar between groups (1.5 ± 0.2 and 1.3 ± 0.1 mg·kg\(^{-1}\)·min\(^{-1}\), Sal and GLP-1, respectively). In response to the hyperglycemic clamp, the liver switched to net glucose uptake in both groups. Although there was no significant difference between groups, there was a tendency for net hepatic glucose uptake to be higher in the GLP-1 group (NHGB = -1.2 ± 0.1 and -1.6 ± 0.2 mg·kg\(^{-1}\)·min\(^{-1}\), Sal and GLP-1, respectively, \(P = 0.52\) during final 2 h) (Fig. 4A). There was no effect of GLP-1 on non-HGU (4.9 ± 1.0 and 4.9 ± 1.2 mg·kg\(^{-1}\)·min\(^{-1}\), final 2 h, Sal and GLP-1, respectively) (Fig. 4B).

**DISCUSSION**

After a meal, the increases in both GLP-1 (7) and glucose levels in the hepatic portal vein are significantly greater than in the peripheral blood. It has been suggested that this elevation of both GLP-1 and glucose must exist for a physiological increase of GLP-1 to exert its effect on glucose utilization (4, 10, 11). We have previously reported that, in the presence of hepatic portal vein glucose infusion, a physiological increase in hepatic portal vein GLP-1 levels of GLP-1 in the hepatic portal vein stimulated Non-HGU via a mechanism independent of changes in pancreatic hormone secretion (11). The results from the present study indicate that, in the absence of a hepatic portal vein glucose infusion, portal vein GLP-1 infusion does not bring about such an effect. This observation is supported by our observation that there was no significant difference in GIR (6.1 ± 1.0 vs. 6.4 ± 1.2 mg·kg\(^{-1}\)·min\(^{-1}\), average over final 2 h, Sal vs. GLP-1, respectively) in the two groups (Fig. 2). The failure of the GIR to rise in the presence of elevated GLP-1 in the absence of portal glucose infusion is explained by the absence of an increase in Non-HGU (4.9 ± 1.0 and 4.9 ± 1.2 mg·kg\(^{-1}\)·min\(^{-1}\), final 2 h, Sal and GLP-1, respectively) (Fig. 4B). In our previous study, the presence of a portal glucose infusion GLP-1 delivery significantly increased (3.8 ± 0.7 to 5.5 ± 0.8 mg·kg\(^{-1}\)·min\(^{-1}\)) Non-HGU (11).

The question thus arises as to the mechanism by which a physiological increase in hepatic portal vein GLP-1 levels resulted in an increase in Non-HGU in the presence of portal glucose infusion GLP-1 delivery (11).
might bring about increased whole body glucose uptake solely in the presence of intraportal glucose delivery. Elevation of portal vein glucose decreases vagal firing by afferent fibers originating in the wall of the hepatic portal vein (16, 20). Portally delivered GLP-1, on the other hand, increases neural firing in afferents originating in the hepatoportal region (17, 25). It has been clearly shown that the portal glucose delivery is associated with a decrease in Non-HGU (9, 14). Thus, if GLP-1 were to override the impact of portally delivered glucose on vagal afferent firing to nonhepatic tissue, one would predict an increase in Non-HGU. Since our laboratory’s earlier work has suggested that the effect of the portal signal occurs in muscle, it seems likely that this is the site of the GLP-1-induced effect (9).

Our laboratory’s earlier data (7) showed that intraportal infusion of GLP-1 (1 pmol·kg⁻¹·min⁻¹) in the presence of hyperglycemia, induced by peripheral glucose infusion, and a pancreatic hormone clamp resulted in a small increase in net hepatic glucose uptake (∼0.8 mg·kg⁻¹·min⁻¹), but no change in Non-HGU. This agrees with data from the present study in which animals that received glucose only via the peripheral route tended to have slightly greater net hepatic glucose uptake when GLP-1 was given intraportally than when it was not (NHGB = −1.6 ± 0.2 vs. −1.2 ± 0.1 mg·kg⁻¹·min⁻¹, GLP-1 vs. Sal, during final 2 h, not significant, \( P = 0.16 \)) (Fig. 4A). As noted in our earlier study (11), in the presence of intraportal glucose infusion, GLP-1 delivery also tended to have a small, direct effect on the liver. Collectively, therefore, our data suggest that physiological increases in GLP-1 can have a direct, albeit small, stimulatory effect on the liver.

It has been well established that exogenously infused GLP-1 acts as an incretin in both healthy humans and those with Type 2 diabetes (19). As noted above, however, in the past (11), as well as in the present study, there was no difference in arterial or portal plasma insulin levels in the presence or absence of GLP-1 infusion. This agrees with earlier data that showed that dogs that received a systemic infusion of glucose to simulate postprandial peripheral glucose levels showed no change in insulin levels when GLP-1 was infused peripherally to create a physiological increase in its level (10). The fact that a physiological elevation in GLP-1 did not result in changes in pancreatic hormone levels in blood in the dog was discussed at length in our previous publication (11); however, a recent study indicates that, upon stimulation of endogenous GLP-1 release in the rat, total levels of GLP-1 in the hepatic portal vein are less than those in the lymph draining from the gut (6).

In our present study, an increase in the intestinal lymph GLP-1 level presumably did not occur, since the elevation in GLP-1 was brought about by infusion. To the extent that lymph GLP-1 is involved in the incretin effect of the peptide, that effect would be absent when the hormone is infused intraportally. On the other hand, numerous investigators (3, 13, 18, 23) have infused GLP-1, presumably in the absence of a rise in lymph GLP-1 levels, and yet they observed an incretin effect of the peptide. The impact, it any, of the increased lymph GLP-1 remains to be clarified.

In conclusion, we have shown that a physiological elevation of plasma GLP-1 in the hepatic portal does not increase whole body glucose utilization when hyperglycemia is induced by peripheral glucose infusion alone. The data presented here, combined with evidence from our earlier study, thus suggest that the GLP-1 secretion that occurs following feeding, when a glucose gradient exists between the periphery and the hepatic portal vein, plays a role in limiting postprandial hyperglycemia. This occurs by increasing glucose utilization independently to form the incretin effect of the peptide.

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**DISCLOSURES**

A. D. Cherrington has consultancies with Merck, and Novo Nordisk; is on the Scientific Advisory Board of Amylin and owns stock in Amylin.

**REFERENCES**


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