Effects of exogenous insulin on glucose tolerance in alpacas

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**Objective**—To evaluate the effects of exogenous insulin on clearance of exogenous glucose in alpacas.

**Animals**—7 adult castrated male alpacas.

**Procedure**—Prior to each of 2 trials, food was withheld for 8 hours. Glucose (0.5 g/kg of body weight) was then administered by rapid IV infusion. During 1 of the trials, regular insulin (0.2 U/kg, IV) was also administered 15 minutes later. Blood was collected immediately before (0) minutes and 15, 20, 25, 30, 45, 60, 90, 120, 180, and 240 minutes after glucose administration. Plasma concentrations of glucose and lactate were determined, and glucose fractional turnover rate and plasma half-life were calculated.

**Results**—Insulin treatment caused a significant increase in fractional turnover rate of glucose and plasma lactate concentration. Plasma glucose concentrations were less in insulin-treated alpacas from 30 minutes after glucose administration (15 minutes after insulin administration) until the conclusion of each trial, compared with nontreated alpacas. In addition, plasma glucose concentration in insulin-treated alpacas returned to baseline values 1 hour sooner than in the nontreated group.

**Conclusions and Clinical Relevance**—Glucose uptake in alpacas improves after insulin treatment, suggesting that administration of exogenous insulin will increase the therapeutic and decrease the pathologic effects of exogenous glucose administered to hypoglycemic alpacas. However, alpacas and other New World camelids should be monitored carefully during treatment with glucose or insulin, because these species appear to be partially insulin resistant. (Am J Vet Res 2001;62:1544–1547)

Insulin is used to treat many disorders of energy metabolism in domestic animals, including diabetes mellitus, ketosis, and hepatic lipodipsia. It has also been used, without proof of efficacy, to treat possible diabetes mellitus, insulin lipodipsia, hyperosmolar disorder, and other hyperglycemic or hyperlipemic conditions in llamas and alpacas. Similarly, glucose is often administered to anorectic or hypoglycemic camelids according to protocols developed to supply energy to other species. However, blood insulin concentrations are less and clearance rates of exogenous glucose are slower in llamas and alpacas, compared with other domestic ruminants. The greatest difference is in insulin concentration. Blood insulin concentration in ruminants often increases 4- to 5-fold after glucose challenge, whereas in New World camelids, blood glucose concentration only doubles. Moreover, plasma insulin concentrations in camelids in response to exogenous administration of glucose (stimulated insulin concentrations) remain less than concentrations in ruminants from which food has been withheld (fasted concentrations). These findings indicate that mechanisms to increase insulin-dependent uptake of glucose are different in camelids than in other species such that exogenous glucose in New World camelids is poorly assimilated. Therefore, exogenous glucose may be of limited therapeutic value to camelids and may even induce pathologic effects on hydration and blood osmolality.

In most mammalian species, insulin is produced and released in response to hyperglycemia. It binds to surface receptors, which in turn promote the movement of a particular cytoplasmic glucose transporter to the cell surface, thereby increasing the ability of the cell to take up glucose. If glucose transport into cells is excessive, the capacity for complete oxidation is overwhelmed, and some glucose is converted to lactate. It is not known whether camelids simply have low insulin concentrations or whether they also lack other components of the insulin-dependent glucose transport system. If the former were true, exogenous insulin could be given in conjunction with glucose to promote cellular uptake. However, in the latter case, insulin treatment would have little effect on glucose kinetics. The purpose of the study reported here was to evaluate the effects of exogenous insulin on clearance of exogenous glucose in alpacas.

**Materials and Methods**

**Alpacas**—Seven adult castrated male alpacas were used. All had been maintained on pasture and supplemented with orchard grass hay for several months. Alpacas were acclimated to stalls and feeding areas for 96 hours before the study and judged to be healthy on the basis of history and results of physical examination, CBC, and serum biochemical analyses. A 16-gauge double-lumen IV catheter was placed into the right jugular vein of each alpaca 2 days before the study. Before and between trials, alpacas were housed in groups to minimize stress.

**Experimental design**—This study was conducted with approval of the Institutional Animal Care and Use Committee of Oregon State University. For each alpaca, 2 trials were performed on subsequent days. The order in which the trials were performed was determined randomly. Before each trial, food was withheld for 8 hours. A time-0 blood sample was collected into tubes containing sodium fluoride and immediately thereafter, alpacas received a 50% glucose solution (0.5 g/kg of body weight) by rapid (< 10 seconds) injection through 1 lumen of the IV catheter. Subsequent
blood samples (15, 20, 25, 30, 45, 60, 90, 120, 180, and 240 minutes after glucose injection) were collected through the other lumen of the catheter after discarding the first 5 ml of blood withdrawn. In 1 of the 2 trials, regular insulin (0.2 U/kg) was also administered IV immediately following collection of the 15-minute blood sample. After both trials were completed, the jugular catheters were removed, and alpacas were fed and returned to the herd.

Determination of plasma glucose and lactate concentrations—Blood samples were placed on ice, and fluoridated plasma was separated from erythrocytes within 20 minutes of collection. Samples were analyzed for glucose and lactate concentration by use of an automated chemistry analyzer.

Determination of glucose and kinetics—The fractional turnover rate of glucose (glucose disappearance rate; \( k \)) was calculated for each interval after insulin administration, using the formula:

\[
k (\% / \text{min}) = \frac{\ln [\text{glucose}]_1 - \ln [\text{glucose}]_2}{\text{interval}_{\text{min}}} \times 100
\]

Fractional turnover rate and plasma half-life (T_{1/2}) of glucose were also calculated for the period from 15 to 45 minutes after glucose infusion. Plasma half-life was determined by use of the formula:

\[
T_{1/2} (\text{min}) = \frac{0.693}{k} \times 100
\]

Statistical analyses—Data were expressed as mean ± SD. Effects of time and insulin on plasma concentrations of glucose and lactate were analyzed by use of 2-way ANOVA for repeated measures. Differences between mean values were assessed by use of the Tukey test. Fractional turnover rates for each interval were also compared between insulin-treated and untreated alpacas by use of a 2-way ANOVA for repeated measures and the Tukey test. Fractional turnover rate and T_{1/2} of glucose determined for the period from 15 to 45 minutes after glucose infusion were compared between insulin-treated and untreated alpacas by use of a paired t-test. For all tests, differences were considered significant at \( P < 0.05 \).

Results

Glucose concentration—Mean plasma glucose concentrations differed significantly (\( P = 0.013 \)) between trials. In addition, the interaction of treatment and time significantly (\( P < 0.001 \)) affected glucose concentration. Glucose concentrations at 0 (preinfusion) or 15 (postglucose, preinsulin) minutes did not differ between trials. However, beginning 15 minutes after insulin injection (30-minute sample) until completion of the trial, mean glucose concentrations in alpacas treated with glucose and insulin were less than in alpacas treated with glucose alone (Fig 1). Glucose concentrations in alpacas treated with insulin returned to preinfusion values within 3 hours, whereas concentrations in alpacas treated with glucose alone returned to preinfusion values within 4 hours.

Glucose kinetics—A significant (\( P = 0.010 \)) difference in fractional turnover rate of glucose was detected between treatment trials. Again, the interaction of treatment and time significantly (\( P < 0.001 \)) affected turnover rate. In alpacas treated with glucose and insulin, mean fractional turnover rates were significantly higher for the first 5 intervals or 45 minutes, compared with alpacas treated with glucose alone (Fig 2). Mean fractional turnover rate peaked at 1.38 ±
0.54%/min in alpacas that received insulin and at 0.83 ± 0.47%/min in alpacas that did not. The turnover rate determined for the period from 15 to 45 minutes after glucose infusion was also significantly (P = 0.007) higher in alpacas that received insulin (1.08 ± 0.28%/min), compared with those that did not (0.63 ± 0.06%/min). Finally, plasma glucose T1/2 in insulin-treated alpacas (69 ± 19 minutes) was significantly (P = 0.001) less than in untreated alpacas: (111 ± 11 min).

**Lactate concentration**—Mean lactate concentrations differed significantly (P = 0.020) between trials. In alpacas treated with glucose only, lactate concentrations decreased over time (Fig 3). However, in insulin-treated alpacas, mean lactate concentrations increased transiently after insulin injection and were significantly (P < 0.036) greater from 30 to 60 minutes (ie, 15 to 45 minutes after insulin injection) after glucose infusion, compared with alpacas treated with glucose alone.

**Discussion**

On the basis of these findings, we conclude that alpacas clear exogenous glucose slowly, not only because of the previously described poor insulin response, but also because of a limited cellular capacity to increase glucose uptake in the presence of insulin. Despite the weak endogenous insulin response to hyperglycemia that has been described in alpacas and other camelids, glucose clearance (ie, glucose plasma T1/2 and fractional turnover rate) increased following insulin administration, indicating that alpaca cells possess insulin receptors and insulin-responsive glucose transporters that do play a role in glucose metabolism. However, insulin-assisted glucose clearance determined in the present study was slower (mean T1/2 [35 minutes], 69 minutes) than unassisted clearance in clinically normal dogs (25 minutes) and cattle (33 minutes). Thus, alpacas are relatively resistant (ie, less sensitive) to the effects of exogenous insulin, compared with other species. Our findings are supported by results of other researchers who used a small number of alpacas and a different model to study insulin resistance and are similar to results obtained for Old World camels. We believe that because camelids have low insulin concentrations and are relatively insulin resistant, skeletal muscle and other insulin-sensitive tissues use fatty acids rather than glucose for energy. Glucose is thus preserved for glucose-dependent tissues (eg, brain, fetus). This alteration in glucose metabolism may be an adaptation to the intermittent availability of feed and the likelihood of starvation in the native environments of New World camels. However, although these alterations do not appear to impair health under normal conditions, disorders of energy metabolism may develop in alpacas under different conditions than would be expected for other domestic animals. In addition, should disorders of energy metabolism develop, effective treatment will likely be different for camelids, compared with other species.

Measurement of plasma lactate concentrations provided an indirect measure of cellular glucose uptake. In many species, glucose tolerance testing leads to an increase in lactate production, because excess intracellular glucose is incompletely oxidized to lactate by extrahepatic tissues. This increase does not occur during glucose tolerance testing in healthy llamas and alpacas, suggesting that extrahepatic tissues in these animals assimilate exogenous glucose poorly. On the basis of results of the present study, poor glucose assimilation (measured as low glucose clearance and high lactate concentrations) can be overcome to some degree by the administration of exogenous insulin. However, as judged by the peak lactate concentration, exogenous glucose assimilation was less in insulin-treated alpacas than in untreated members of other species.

Even though alpacas have low concentrations of endogenous insulin, fractional turnover rates of glucose are less and clearance half-times of glucose are longer in clinically normal alpacas than in dogs with type-I or type-II diabetes mellitus. This suggests that other mechanisms of glucose clearance, such as insulin-independent cellular uptake or renal loss, are active in alpacas. Urinary glucose loss has been documented in Old World camels after IV infusion of glucose. The renal threshold for glucose excretion has not been established in alpacas. However, from our experience, it is likely to be low, and renal loss of glucose is likely to be an important mechanism by which camelids avoid chronic hyperglycemia.

Our data suggest that although the response was weak, insulin may be administered in conjunction with glucose to improve glucose assimilation and avoid pathologic changes in osmolality. However, more research is necessary to determine the correct protocols for insulin and glucose administration in alpacas. In addition, it cannot be ascertained from our results whether insulin can be used to treat naturally occurring hyperglycemia. The action of regular insulin lasted for 45 minutes and enabled a more rapid return to baseline plasma glucose concentrations. Administration of higher insulin doses would be unlikely to improve glucose uptake to a greater degree, because the dose we used was the same used to treat hyperglycemia in other species. This dose should have resulted in blood insulin concentrations far in excess of those necessary to saturate receptors. Administration of longer acting forms, repeated doses, or slow infusions of insulin may allow for greater glucose assimilation but may also induce hypoglycemia in camelids that do not receive exogenous glucose. Therefore, careful monitoring of plasma glucose concentrations during and after glucose or insulin administration in camelids is recommended to avoid pathologic changes in blood glucose concentrations or osmolality.

References