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ORIGINAL PAPER

Absence of exendin-4 effects on postprandial glucose and lipids in the Gila monster, *Heloderma suspectum*

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Abstract Circulating nutrients serve as energy resources for functioning tissues throughout the body. While the tight regulation of plasma nutrients has been extensively studied in mammals, investigations into specific metabolic regulators in reptiles have been limited and have revealed conflicting results. The peptide exendin-4, which was isolated from the saliva of Gila monsters, *Heloderma suspectum*, has demonstrated prolonged plasma glucose-lowering properties in mammals. Although exendin-4 has often been labeled a venom protein, circulating plasma levels of exendin-4 have been shown to increase in response to feeding. Because exendin-4 has glucose-regulating effects in mammals, we hypothesized that post-prandial elevation in circulating exendin-4 levels in Gila monsters reduces plasma glucose and triglycerides. To examine the effect of exendin-4 on circulating nutrients, we measured plasma glucose, triglyceride, and cholesterol levels of Gila monsters in response to one of four treatments: fed live mice (a natural post-prandial increase in exendin-4), force-fed dead mice while anesthetized (no post-prandial exendin-4 increase), force-fed dead mice while anesthetized and injected with exendin-4 immediately after feeding (exogenous increase in exendin-4), and force-fed dead mice while anesthetized and injected with exendin-4 24 h after feeding (delayed exogenous increase in exendin-4). After prey ingestion, glucose and triglyceride levels increased significantly over time in all treatment groups, but there was no significant treatment effect. Plasma exendin-4 levels showed significant time and treatment effects, but did not correspond to glucose and triglyceride levels. Our results demonstrate that plasma nutrient levels in Gila monsters respond relatively slowly to feeding and that exendin-4 does not have the same effect on circulating glucose in Gila monsters as it does in mammals. Further studies are necessary to determine whether circulating exendin-4 has an alternate role in regulating other components of energy metabolism such as nutrient uptake rate in the small intestine.

Keywords Exendin-4 · Glucose · Triglyceride · *Heloderma suspectum* · Nutrient regulation

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Introduction

Regulation of circulating nutrients is critical to assure adequate energy resources for functioning tissues throughout the body. In mammals, plasma glucose levels are carefully regulated by a counter-balancing of the glucose-raising effects of glucagon and the glucose-lowering effects of insulin (Schreibman et al. 1993). These two hormones are also important in the regulation of lipid processing and plasma triglycerides (Schreibman et al. 1993). In reptiles, the regulation of circulating nutrients by insulin and glucagon is much less clear. Reptiles are of particular interest not only because they represent an ancestral system but also because energy resource regulation is likely under different selective pressures due to their much lower metabolic rate.

It is generally accepted that most reptile species produce insulin and glucagon. However, investigations into their specific roles as glucose and triglyceride regulators in reptiles have been limited and have revealed conflicting results. Little is known about the effects of insulin on lipid metabolism in any reptile taxon. Glucagon may be a more predominant glucose regulator in reptiles as it has hyperglycemic properties in representatives of all major reptile taxa including squamates (i.e., snakes and lizards), crocodilians, and turtles (Penhos and Ramey 1973). For example, in fasting lizards (*Varanus exanthematicus*) circulating glucagon levels are high but drop after feeding (Godet et al. 1984). Similarly, in fasting turtles insulin levels are low and glucagon levels are high (Dupegodet and Adjovi 1981a, b). Furthermore, pancreatectomy induced hypoglycemia in snakes (Houssay and Penhos 1960) and lizards (Penhos et al. 1965). This result is supported by the fact that the pancreas of some snakes and lizards has predominantly glucagon producing α-cells (Penhos and Ramey 1973). However, pancreatectomy in turtles and alligators induces hyperglycemia (Aldehoffe 1891; Penhos et al. 1967). Circulating resting blood glucose levels also differ among groups; lizards exhibit high glucose levels ranging from 100 to 300 mg/dl, while snakes, turtles, and crocodilians have a lower range of 50–100 mg/dl (Chester-Jones et al. 1987). These taxon-specific differences may suggest that the predominant metabolic regulator varies phylogenetically, although other characteristics such as diet may be responsible for the differences seen in the limited number of species studies.

One potential species-specific metabolic regulator may be the peptide exendin-4, which was isolated from the saliva of Gila monsters, *Heloderma suspectum* (Eng et al. 1992), and has shown plasma glucose-lowering activity in mammals. While exendin-4 is encoded by a distinctly separate genetic sequence from mammalian and H. suspectum proglucagon (Chen and Drucker 1997), its actions are much like those of glucagon-like peptide 1 (GLP-1), which stimulates insulin secretion and inhibits glucagon secretion. Exendin-4 binds to pancreatic islet GLP-1 receptors and does so with a higher affinity than GLP-1, therefore prolonging the effects of the receptor system (Goke et al. 1993; Montrose-Rafizadeh et al. 1997). Several studies using obese rats, mice, and primates as diabetic models have show that exendin-4 effectively reduces blood glucose levels for prolonged periods (Young et al. 1999a; Szayna et al. 2000). Human clinical trials have indicated a similar trend (Egan et al. 2002), and synthetic exendin-4 is currently available as a prescription drug (Byetta, Amylin Pharmaceuticals, Inc.) for treatment of type-II diabetes.

While exendin-4 was initially considered a venom component used in the acquisition of prey, Young et al. (1999b) demonstrated the existence of high plasma exendin-4 levels in the Gila monster after feeding which suggests a physiological role of exendin-4 in digestive performance and/or metabolic regulation. Unfortunately, no studies have assessed the effect of exendin-4 on circulating nutrients in its native organism. Energy regulation in the Gila monster is especially intriguing because Gila monsters naturally eat very large meals (primarily eggs and rodent/rabbit neonates) at infrequent intervals. Such a binge-feeding diet leads to dramatic shifts in nutrient availability and has been associated with major changes in the anatomy and physiology of the digestive tract. Pythons, which are also infrequent feeders that consume large meals, show dramatic changes in gut morphology and nutrient uptake rates after feeding (Secor and Diamond 1995; Lignot et al. 2005). Additionally, post-prandial cardiac function increases considerably more in pythons than other animals (Secor et al. 2000). While anatomical and physiological changes can be extensive in species that eat infrequent large meals, few studies have examined the hormonal regulators of such changes. In one exception, Secor et al. (2001) using pythons, demonstrated a significant post-prandial elevation in circulating levels of several gastrointestinal regulatory peptides including glucagon. The authors suggest that the post-prandial increase in plasma glucagon seen in pythons, which is in contrast to the post-prandial glucagon decrease typical of mammals, is a result of the high protein content of their meals (Secor et al. 2001). Even though exendin-4 has glucose-regulating effects via the GLP-1 receptor in mammals, the glucagon paradox in pythons, a reptile with a similar feeding strategy, may indicate that exendin-4 has alternative physiological effects in Gila monsters. Therefore, we investigated whether exendin-4 has an effect on glucose and triglyceride regulation in the Gila monster. We hypothesized that post-prandial elevatation in circulating exendin-4 levels in Gila monsters reduce plasma glucose and triglycerides. To test our hypothesis, we experimentally manipulated post-prandial plasma exendin-4 levels and measured circulating glucose, triglyceride, and cholesterol levels after ingestion of whole prey.

Methods

Animals and housing

Twenty-four adult Gila monsters, *Heloderma suspectum* (15 male and 9 female, mass range 304–670 g) acquired

from the Arizona Game and Fish Department (current holding permit number: SP727850) were used for this experiment. Gila monsters were pair-housed in cages (90 cm width × 70 cm diameter × 45 cm height, Vision Products, Canoga Park, CA, USA) and maintained at a room temperature of 25°C. Cages were equipped with a 40 W incandescent lamp at one end of the cage that created a thermal gradient of 23–45°C, PVC refugia, and a bowl to provide water ad libitum.

Whole prey ingestion

Previous work demonstrated significant elevations in plasma exendin-4 levels after biting or feeding on rodent prey; however, there was no significant increase in plasma exendin-4 when prey were force-fed to Gila monster while the lizards were anesthetized (Christel and DeNardo 2006). We used four treatment groups ($n = 6$ per group) based on these previous results to evaluate the effect of exendin-4 on circulating glucose and triglyceride levels after ingestion of natural prey. All treatment groups ingested the same prey, yet plasma exendin-4 levels were varied by treating the subjects in four different ways: (1) fed three live mice (endogenous exendin-4 increase, positive control, POS), (2) force-fed while anesthetized three dead mice (no exendin-4 increase, negative control, NEG), (3) force-fed while anesthetized three dead mice and injected with exendin-4 immediately after feeding (EX-0 h), (4) force-fed while anesthetized three dead mice and injected with exendin-4 24 h after feeding (EX-24 h). Treatments were administered randomly over a three-day period and at an ambient temperature of 26°C. For the POS group, we placed each Gila monster individually in a plastic box ($25 \times 35 \times 14$ cm^3) with three live sub-adult mice (approximately 20 g each, range 19.8–20.9 g), which they consumed within 15 min. To prevent endogenous exendin-4 from increasing during feeding in the NEG, EX-0 h, and EX-24 h groups, we lightly anesthetized each Gila monster by placing it in a chamber containing isoflurane until it was unresponsive to touch. We then fed it three dead sub-adult mice (approximately 20 g each, range 19.5–21.3 g) using a bird speculum to keep the mouth open and a pair of hemostats to push the mice into the stomach. For the exendin-4 injection treatment groups, we intracoelomically injected each animal with 17.5 μg/kg exendin-4 (100 μg/ml in sterile water) to mimic normal post-prandial plasma levels (typically 20–30 ng/ml plasma, unpublished data). We injected the EX-0 h group with exendin-4 immediately after ingestion of the mouse pups. The EX-24 h group was injected with exendin-4 after the 24 h-blood sample was taken to create a situation where normal post-prandial exendin-4 levels were delayed. For the POS and NEG groups, we took blood samples from each animal before feeding (time 0) and at 2, 24, 48, and 72 h after feeding. For the EX-0 h treatment group, we took blood samples from each animal before feeding (time 0) and at 2, 24, and 48 h after feeding and exendin-4 treatment. For the EX-24 h treatment group, we took blood samples from each animal before feeding (time 0) and at 24, 26, 48, and 72 h after feeding. These blood collection schedules were based on pilot studies and designed to assess acute plasma nutrient changes (i.e., 2 h post-treatment) as well as more prolonged plasma nutrient changes at 24 h intervals since metabolic responses in reptiles, including Gila monsters (unpublished data) are often delayed. These sampling intervals also provided assessments of plasma exendin-4 levels 2 h after feeding or exogenous exendin-4 treatment, which is the time when exendin-4 levels peak (Young et al. 1999a; Christel and DeNardo 2006, unpublished). While additional sampling would have been advantageous for assessing temporal patterns in plasma nutrient levels, the total amount of blood we could collect from the animals was limiting (approximately 0.6 ml per sample, total volume could not exceed 1% of body mass). Blood samples were collected from the caudal tail vein using heparinized 1 ml syringes. Within 15 min of collection, we separated plasma from whole blood via centrifugation and stored it at −80°C until analysis at Amylin Pharmaceutical for glucose, triglyceride, cholesterol, and exendin-4 concentrations.

Analysis of plasma glucose, triglyceride, cholesterol, and exendin-4 concentrations

Plasma glucose, triglycerides, and cholesterol were measured using a Cobas Mira Plus chemistry analyzer (Roche Diagnostics Corporation, Indianapolis, IN, USA), which uses absorbance photometry to measure the metabolites. Plasma exendin-4 was measured using a two-site sandwich immunoenzymetric assay (IEMA) with fluorescent detection as described by Christel and DeNardo (2006). Briefly, plasma samples, exendin-4 standards, and plasma controls were added to microtiter plate wells coated with monoclonal antibody EXE4: 2–8.4. After a 2 h incubation period, biotinylated monoclonal detection antibody GLP1: 3–3.1 was added, and a signal was generated by the addition of an alkaline phosphatase substrate. The fluorescent signal was detected with a microplate fluorometer, and concentrations of exendin-4 in plasma samples were determined by comparison with the calibration curve calculated from the exendin-4 standards.

Statistical analysis of results

Using SAS, we analyzed differences in glucose, triglyceride, cholesterol, and exendin-4 level among groups and over time (for time points 0, 2, 24, 48, and 72 h) using repeated measures analysis of variance (RMANOVA, $\alpha = 0.05$) with treatment group as the between-subjects factor, time as the within-subjects factor, and glucose, triglyceride, cholesterol, or exendin-4 level as the dependent variable. In addition for the glucose and triglyceride levels, we used a paired *t* test for means ($\alpha = 0.05$) to assess the differences between the 24 and 26 h samples in the EX-24 h group.

Results

After prey ingestion, glucose levels increased significantly over time ($F_{4,70} = 37.3$, $P \leq 0.0001$), but there was no significant treatment effect ($F_{3,20} = 0.3$, $P = 0.82$) or a time by treatment interaction ($F_{10,70} = 1.2$, $P = 0.30$, Fig. 1a). Additionally, there was no difference in plasma glucose levels at 24 and 26 h for the EX-24 h group ($P = 0.43$). Similarly, triglyceride levels significantly increased over time ($F_{4,70} = 25.7$, $P \leq 0.0001$), but there was no significant treatment effect ($F_{3,20} = 0.8$, $P = 0.50$) or a time by treatment interaction ($F_{10,70} = 0.8$, $P = 0.68$, Fig. 1b). There was also no difference in the plasma triglyceride levels at 24 and 26 h for the EX-24 h group ($P = 0.43$). Cholesterol levels averaged 150 mg/dl (range of 56–517 mg/dl) and did not change significantly over time ($F_{4,70} = 0.8$, $P = 0.51$) and did not significantly differ among treatment groups ($F_{3,20} = 0.2$, $P = 0.90$, Fig. 1c).

Plasma exendin-4 levels showed significant time ($F_{5,74} = 83.6$, $P \leq 0.0001$) and treatment ($F_{3,20} = 5.1$, $P = 0.0085$) effects, as well as a time by treatment interaction ($F_{10,74} = 4.2$, $P = 0.0001$). Plasma exendin-4 level substantially increased in the POS and EX-0 h groups and slightly increased in the NEG group post-feeding (Fig. 1c). The significance of the increased exendin-4 levels in the NEG group is due to one Gila monster in this group having high exendin-4 at 2 h (10,200 pg/ml). Plasma exendin-4 levels of the EX-24 h group were significantly elevated at 26 h, 2 h after the 24-h injection (Fig. 1d). Overall, except for in one animal in the NEG group, plasma exendin-4 levels responded as designed, effectively distinguishing the four treatment groups.

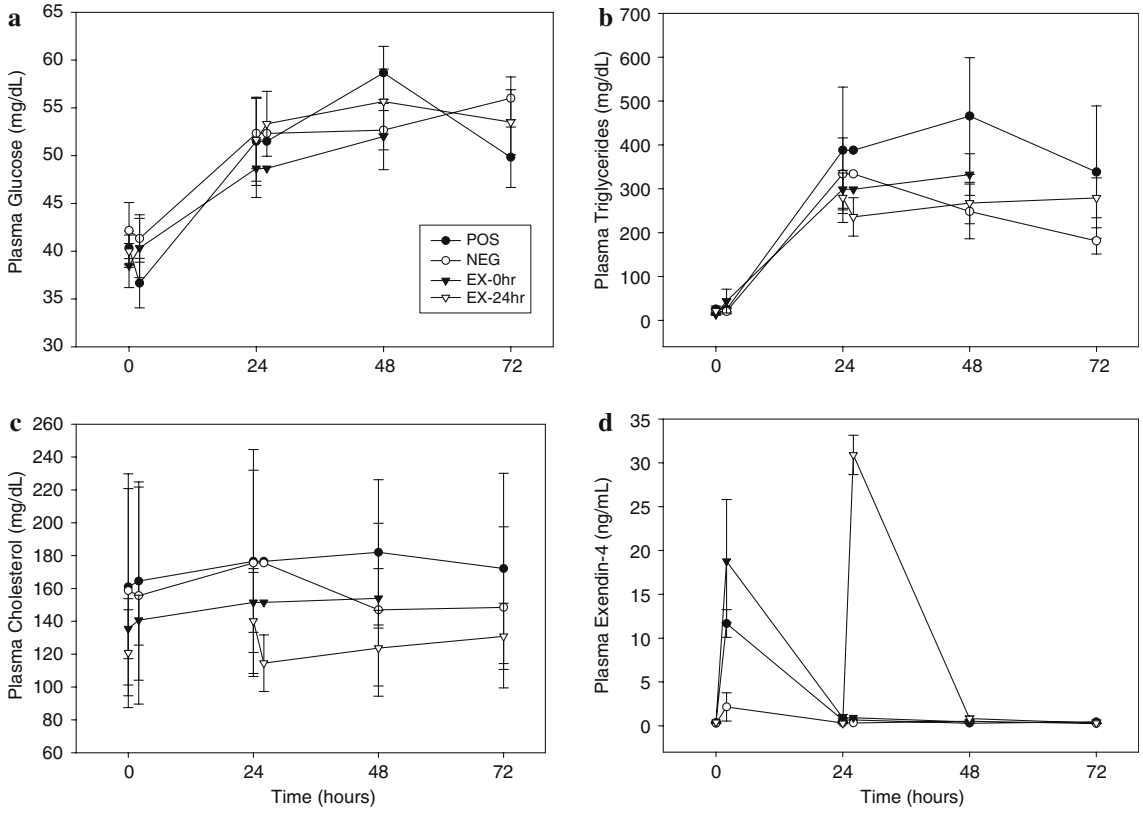

Fig. 1 Circulating (**a**) glucose, (**b**) triglyceride, (**c**) cholesterol, and (**d**) exendin-4 levels of the four treatment groups from the time of feeding (time 0). *Symbols* represent group means and *vertical lines* represent standard error

Discussion

Temporal patterns in circulating nutrient levels

Gila monsters fed whole prey experienced a slight but significant increase in plasma glucose levels and a large increase in plasma triglyceride levels, with both changes following a temporal pattern that is different from most mammals. Mammals rapidly begin digestion and absorption of meal components, which leads to increased circulating nutrients within 1 h of feeding (Keneko 1980). Post-prandial increases in plasma glucose level are typically 50–100 mg/dl, but circulating levels quickly return to a normoglycemic level of 75–100 mg/dl (Keneko 1980). In this study, Gila monsters showed no change in plasma glucose levels by 2 h post-feeding but rather had a slowed and limited post-prandial increase of 20 mg/dl of glucose that did not return to pre-prandial levels (~38 mg/dl) over the 72 h study period. Plasma triglyceride levels showed a temporal pattern that was similar to plasma glucose, but the magnitude of the change in circulating triglyceride levels was much greater. On average across treatment groups, plasma triglycerides increased from 20 to 300 mg/dl, a 15-fold increase. One possible explanation for the prolonged effects and the difference in the magnitude of the responses may be the size and composition of the diet. Mice are composed predominantly of protein (45–65%) and fat (17–30%) with little carbohydrate content (<10%) (Dierenfeld et al. 1994). Although no studies have assessed nutrient/energy processing in Gila monsters, carnivorous ectotherms "may rely primarily on protein and/or lipid metabolites" instead of glucose (Deroos and Rumpf 1987). The dramatic and sustained increase in triglycerides seen in this study may lend support for this possibility.

While not typical of mammals, the slowed and prolonged plasma nutrient elevation seen in Gila monsters is similar to results from pythons. The Burmese Python (*Python molurus*) requires 5–11 days to complete digestion (Secor 2003) and experiences a significant increase (160-fold!) in plasma triglycerides 1 day post-feeding (Secor and Diamond 1998). Thus, the patterns in circulating nutrients seen in our study may reflect the Gila monsters' feeding strategy.

Effect of exendin-4 on circulating nutrients

The results of this study demonstrate that exendin-4 does not affect post-prandial plasma levels of glucose and triglycerides in Gila monsters. Elevated exendin-4 levels in the EX-0 h and EX-24 h groups as well as the POS group did not have significantly different levels of either glucose or triglycerides compared to the NEG group that had significantly lower plasma exendin-4 levels. While a positive effect may have been missed by our relatively infrequent sampling, the slow nature of changes in Gila monster plasma nutrient levels make this possibility unlikely. Our results are in sharp contrast to those reported in mammals, in which exendin-4 causes a dramatic reduction in elevated plasma glucose levels. Circulating nutrient levels in Gila monsters may be controlled by alternate hormones, such as GLP-1, for which expression has been demonstrated in the Gila monster gut (Chen and Drucker 1997). However, exploring the role of GLP-1 in the regulation of intestinal function would be facilitated by first characterizing this peptide for Gila monsters.

Why do Gila monsters have exendin-4?

Our study illustrates the postprandial pattern of circulating nutrients in Gila monsters and that this pattern is not influenced by the presence or absence of exendin-4. Therefore, the question remains: what is the role of exendin-4 for Gila monsters? While exendin-4 has been considered a venom component because of its discovery from a "venom" sample (Eng et al. 1992), this assertion is uncertain. First, because of a relatively inefficient delivery system, Gila monster venom and salivary components are mixed within the buccal cavity and thus a venom sample contains a mix of molecules which have functional roles associated with endogenous physiological function or envenomation. Additionally, the only known effect of exendin-4 on rodents (a reduction from hyperglycemia to normoglycemia) does not suggest a prey acquisition role, although it is possible that venom contains exendin-4 in concentrations substantially greater than doses previously reported to have been given to rodents (Young et al. 1999b; Szayna et al. 2000). Second, we are not aware of any reports of other venom proteins that exist in the plasma of the source organism in concentrations as high as those found for exendin-4 in Gila monsters post-prandially. Increases in plasma levels of exendin-4 are associated with chewing (Christel and DeNardo 2006), but this behavior can be associated with defense, prey immobilization, swallowing, and digestion. Thus, it is uncertain whether the post-prandial elevation in plasma exendin-4 has a function or whether it merely reflects passive absorption of salivary components from the oral cavity. Although our results fail to reveal a functional role of circulating exendin-4 in regulating circulating glucose and triglycerides, exendin-4 may have an as yet unidentified role in metabolic, digestion, or absorption events. Future investigations should

examine other potential sites of exendin-4 regulation such as the uptake of nutrients in the small intestine as well as changes in intestinal morphology.

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