Pre-Clinical Evaluation of Glucose-dependent Insulinotropic Polypeptide (GIP) Receptor Agonism as a Treatment for Cancer-Induced Dysregulation of Glucose Homeostasis

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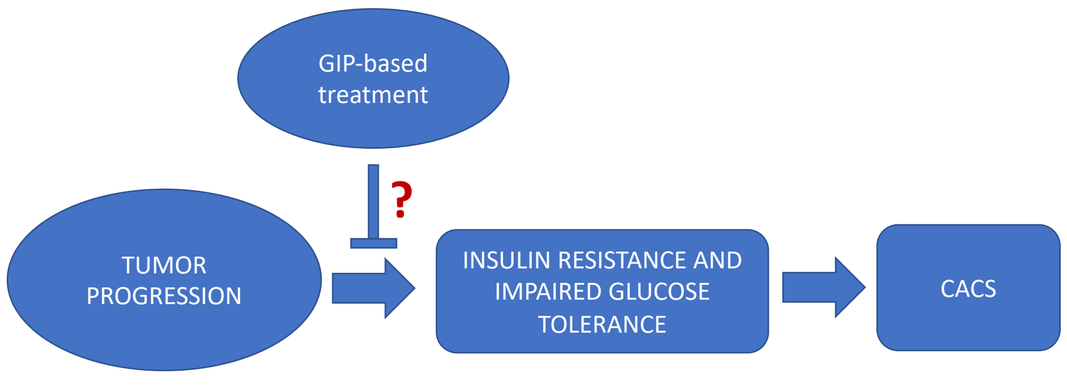
Introduction

Insulin resistance and reduced glucose tolerance are well-known phenomena contributing to the cancer anorexia cachexia syndrome (CACS) and worsen quality of life in patients. Despite its clinical relevance, no pharmacological treatment is yet approved.

Type 2 Diabetes Mellitus (T2DM) and cancer progression have similar metabolic alterations that affect regulation in energetic pathways including insulin resistance and reduced glucose tolerance.

The glucose-dependent insulinotropic polypeptide (GIP), a hormone stimulating insulin release, holds promise for the treatment of cancer-induced dysregulation of glucose homeostasis as it does not induce anorexia, characteristic of other classes of anti-diabetic medications.

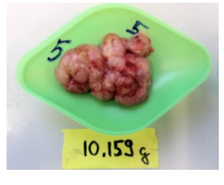


Aims

1. **Assess the effects of chronic GIP receptor agonism on feeding and glucose homeostasis in healthy Buffalo rats**
2. **Characterize the time course of insulin resistance and glucose intolerance in hepatoma tumor-bearing rats**
3. **Test the ability of GIP receptor agonism to counteract tumor-induced insulin resistance and glucose intolerance in rats**

Methods

- Acute and chronic injections of a long-acting GIP analog (LA-GIP) in healthy Buffalo rats
- In vitro cultured Morris-7777 hepatoma cells (10^7 cells/animal) were inoculated to induce subcutaneous tumor growth
- Food intake, body weight, and kaolin consumption (a proxy of malaise in rats) were daily recorded
- Glucose tolerance was assessed weekly using the intraperitoneal injection glucose tolerance test (IPGTT)



In this model, tumors become palpable 8-12 days and reach approx. 10-15g 3 weeks after inoculation.

Results

A single LA-GIP injection reduces glucose levels during an IPGTT in Buffalo Rats

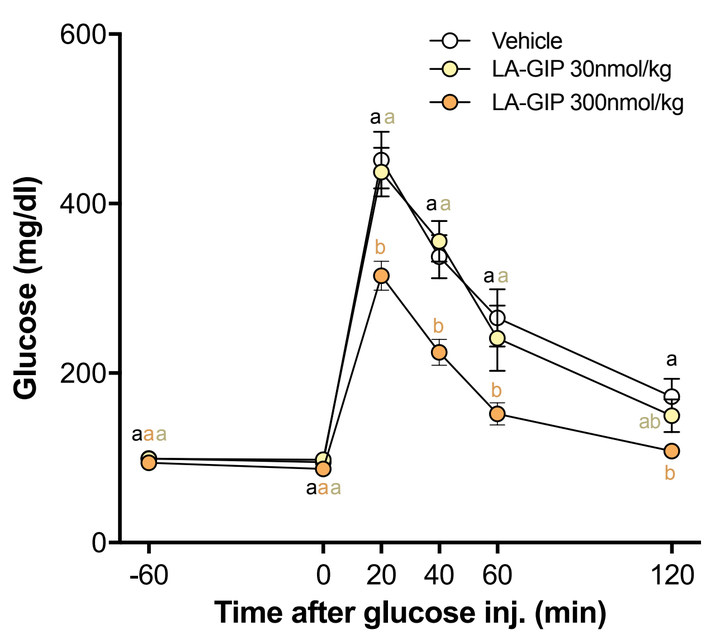
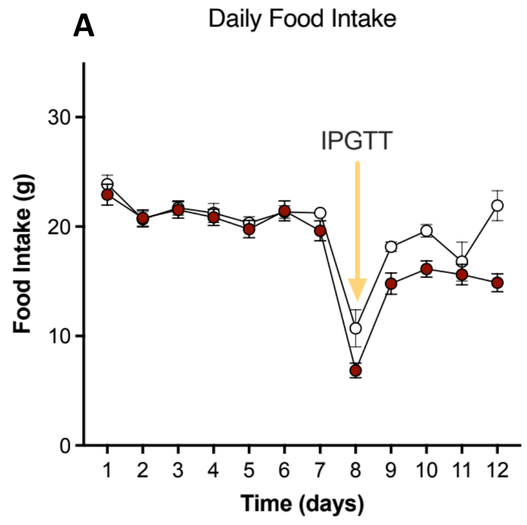
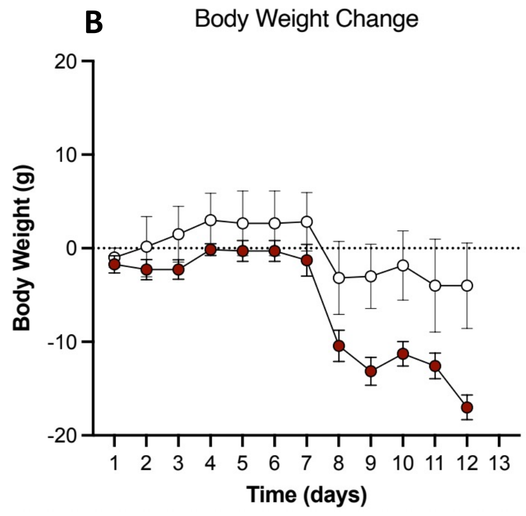


Figure 1: *LA-GIP (30 and 300 nmol/kg, IP, injected at t = -60 min) dose-dependently suppressed blood glucose levels following an intraperitoneal glucose tolerance test (2 g/kg, IP, injected at t = 0) in healthy Buffalo rats (n=11). All data expressed as mean ± SEM and analyzed with repeated measures two-way ANOVA followed by Tukey's post-hoc test. Means with different letters are significantly different from each other (P < 0.05).*

Tumor-Bearing Rats display anorexia, body weight loss and glucose intolerance (ongoing experiment)





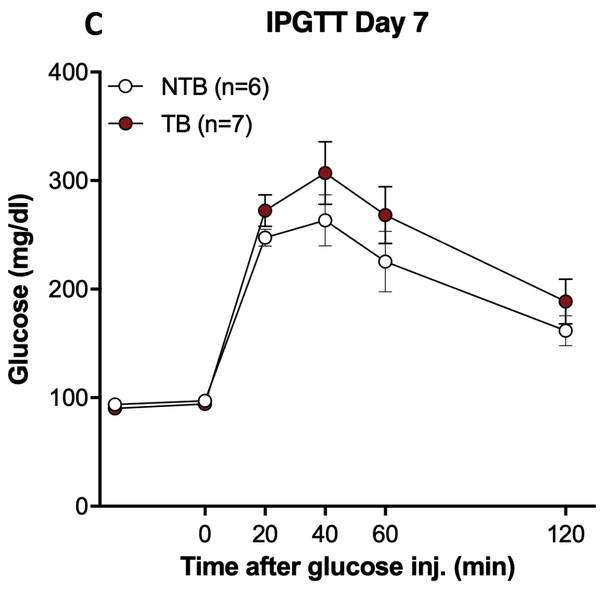
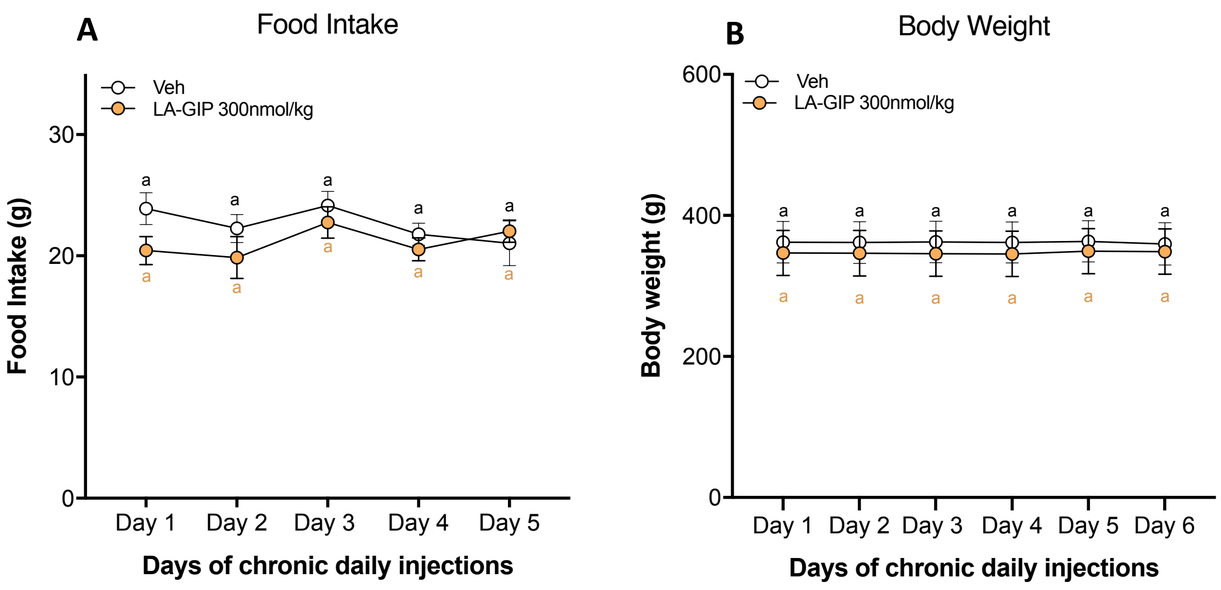


Figure 3: ***A)*** *Tumor-bearing (TB) animals begin to show a decline in food intake compared to controls ~7 days after cell inoculation.* ***B)*** *Similarly, tumor growth-induced anorexia was paralleled by progressive body weight loss.* ***C)*** *Tumor-bearing (TB) animals show a trend towards impaired glucose regulation during an intraperitoneal glucose tolerance test (2 g/kg, IP, injected at t = 0) compared to non-tumor-bearing (NTB) controls (n=6-7 per group). All data expressed as mean ± SEM and will be analyzed with repeated measures two-way ANOVA followed by Siddak's post-hoc test.*

LA-GIP Chronic Administration Retains its Blood Glucose Lowering Effects Without Causing Anorexia nor Body Weight loss



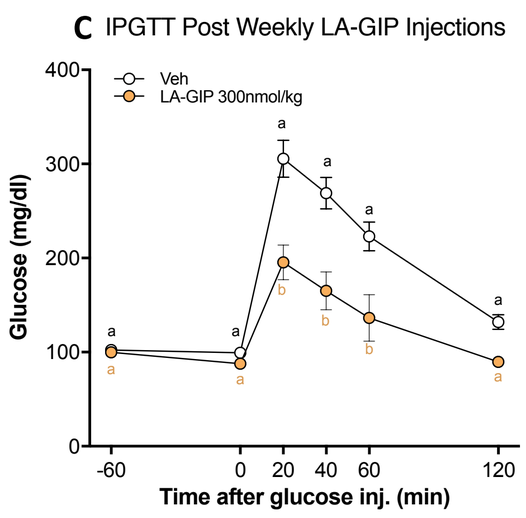


Figure 2: ***A)*** *LA-GIP (300 nmol/kg, IP) daily injections did induce anorexia in healthy Buffalo rats (n=9/group).* ***B)*** *LA-GIP daily administration did not affect body weight (n=9/group).* ***C)*** *LA-GIP (300 nmol/kg, IP, injected at t = -60 min) still suppressed blood glucose levels following an intraperitoneal glucose tolerance test (2 g/kg, IP, injected at t = 0) in healthy Buffalo rats upon chronic administration (n=9/group). All data expressed as mean ± SEM and analyzed with repeated measures two-way ANOVA followed by Tukey's post-hoc test. Means with different letters are significantly different from each other (P < 0.05).*

Conclusion & Outlook

LA-GIP retains its blood lowering properties upon chronic administration without any effects on feeding nor body weight in healthy rats.

Ongoing experiments suggest the presence of impaired glucose homeostasis that precedes the onset of an anorectic response.

Current studies are evaluating the beneficial effect of LA-GIP chronic treatment in tumor-bearing rats.

Future lines of research will include the assessments of malaise to understand whether GIP can also prevent malaise induced by tumor growth. Furthermore, the ability of GIP-based treatments to also prevent muscle loss following tumor growth will also be investigated.

Acknowledgments

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