Unlipidated Anti-obesity Peptides Achieve Body Weight Reductions Similar to Those of Lipidated Counterparts

Guillermo Hails, PhD; Eric L. Schneider, PhD; John A. Hangasky, PhD; Gary W. Ashley, PhD; Christian Weyer, MD, MAS; Daniel V. Santi, MD, PhD.

Background: Incretin- and amylin-based anti-obesity peptides are commonly modified with long-chain fatty-acid albumin-binding moieties that extend elimination half-life from hours to approximately one week through increased plasma protein binding. However, receptor potency and selectivity reside primarily within the peptide pharmacophore itself. We therefore hypothesized that removing the lipid side chain, while maintaining sustained systemic exposure, would preserve maximal anti-obesity efficacy.

Methods: To test this hypothesis, a panel of unlipidated peptide variants corresponding to clinically validated pharmacophores was evaluated in diet-induced obese (DIO) rodents. These included a GLP-1/GIP dual agonist, a GLP-1/GIP/GCG tri-agonist, a dual amylin and calcitonin receptor agonist (DACRA), and a selective amylin receptor agonist (SARA). The unlipidated peptides were administered by subcutaneous osmotic minipumps for several weeks to approximate constant systemic exposure, with infusion rates selected to achieve or exceed concentrations required for maximal pharmacologic activity. Body weight was monitored longitudinally and maximal percent body-weight loss (BWL) achieved was compared with that reported for lipidated counterparts in the same preclinical models.

Results: Across pharmacologic classes, unlipidated peptide variants produced robust, dose-dependent reductions in body weight. At optimized infusion rates, maximal BWL plateaus closely matched those reported for lipidated analogs (tirzepatide, retatrutide, GUBamy, eloralintide, respectively). Maximal BWL values for unlipidated versus lipidated peptides were approximately 25% vs 25-30% for the GLP-1/GIP dual agonist, and 38% vs 35–40% for the GLP-1/GIP/GCG tri-agonist in DIO mice; and 11% vs 10% for the DACRA and 14% vs 12% for the SARA in DIO rats.

Conclusions: These results demonstrate that maximal anti-obesity efficacy is encoded in the native peptide pharmacophore and does not require lipidation when sustained exposure is maintained. By decoupling pharmacodynamics from pharmacokinetics, these findings define the intrinsic efficacy potential of anti-obesity peptide pharmacophores and highlight alternative development strategies—such as long-acting depot formulations—for unmodified peptides.

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Background

Incretin- and amylin-based anti-obesity peptides are commonly modified with long-chain fatty-acid albumin-binding moieties that extend elimination half-life from hours to approximately one week through increased plasma protein binding. However, receptor potency and selectivity reside primarily within the peptide pharmacophore itself. We therefore hypothesized that removing the lipid side chain, while maintaining sustained systemic exposure, would preserve maximal anti-obesity efficacy.

Prolynx's Technology

Prodrug Components:

Hydrogel Microspheres

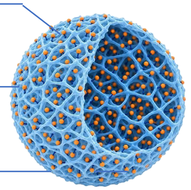
Tetra-PEG polymer (95% water) that can be injected with a small gauge needle and placed subcutaneously

Active Drug Covalently Linked

Covalent linkage to hydrogel matrix enables tightly controlled release of unmodified native drug from depot

Tunable Release and Depolymerization

Finely tuned β-eliminative rate achieves desired release profile for smoother PK and predictable >100 days half-life

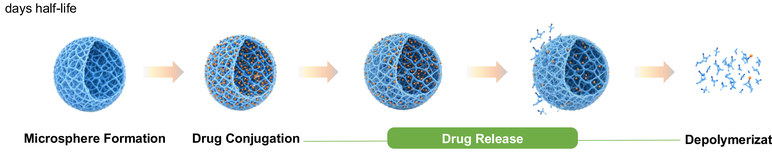


Resulting Pharmacokinetics:

Continuous pump-like release of drug
Results in a smooth PK profile with no burst, thus improving GI tolerability

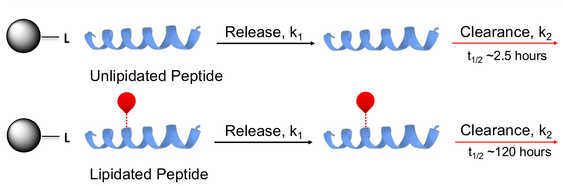
Ultra-long half-life
Determined by the slow release of drug into the circulation, not reduced clearance (as with lipidation)

Potential for monthly and quarterly dosing
Half-life extension is not limited by the half-life of human albumin, breaking past current dose frequency barriers



Lipidation Is Not Required for Half-Life Extension

- Either lipidated or unlipidated peptides can be covalently attached to microsphere (MS).
- MS~Peptide SC depot releases peptide with half-life tuned by β-eliminative linker (k_1).
- Released peptide in the system gets cleared (k_2) with a $t_{1/2}$ ~2.5 hours for unlipidated peptides and a $t_{1/2}$ ~120 hours for lipidated peptides, both adding minimal contribution to the observed $t_{1/2}$.
- The observed half-life is driven by linker cleavage as $k_2 >>> k_1$.



$k_1 <<< k_2$

Peptide half-life driven by linker chemistry, not peptide structure

Prolynx Approach to Drug Development

Identification of API → Modulation and tuning of linker profile → Demonstration of PK and in vivo efficacy

The Prolynx approach to creating novel, long-acting prodrugs relies on three important, universal concepts:

- Identification of novel, potent, highly stable APIs.
- Incorporation of the tunable linker system to develop a prodrug with both the desired release kinetics and depot residence time to achieve the target pharmacokinetics.
- Demonstration of extended half-life and efficacy of the designed prodrug in animal models to directly inform human clinical trials.

Results - Incretins

Continuous Infusion of Unlipidated Peptides Drives Dose-Dependent Body Weight Loss in DIO Mice



Figure 1. Continuous infusion of unlipidated peptides achieve BWL comparable to their lipidated counterparts in C57BL DIO mice (n=5/group). Left: Body weight loss relative to vehicle of a novel unlipidated GLP-1/GIP receptor agonist given at three different infusion rates, 2.5 pmol/h, 25 pmol/h and 250 pmol/h. The two higher infusion rates achieve BWL >25% relative to vehicle, comparable to reported Tirzepatide values [1]. Right: Body weight loss relative to vehicle of a novel unlipidated GLP-1/GIP/GCG receptor agonist given at three different infusion rates, 2.5 pmol/h, 25 pmol/h and 250 pmol/h. The maximum achieved BWL ~35%, relative to vehicle, is comparable to reported Retatrutide values [2]. Data shown as mean ± SEM. Data were analyzed using a mixed-effects model, followed by Dunnett's multiple comparisons test (*p<0.05;***p<0.001).

Continuous Infusion of Unlipidated Peptides Reduce Adiposity in DIO Mice

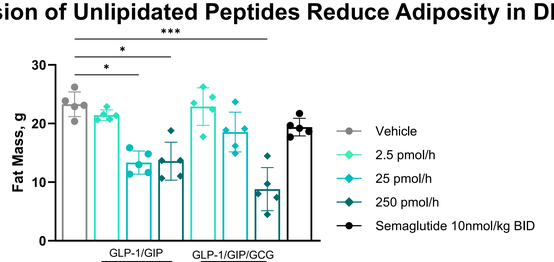


Figure 2. Fat mass in DIO Mice following 28-day continuous infusion. C57BL DIO mice (n=5/group) were infused with either unlipidated GLP-1/GIP receptor agonist or GLP-1/GIP/GCG receptor agonist at infusion rates of 2.5 pmol/h, 25 pmol/h and 250 pmol/h; Vehicle was infused with PBS; Semaglutide (10 nmol/kg) was administered SC BID. DEXA scan was used to assess fat mass on day 28. Data shown as mean ± SEM. Data were analyzed by Kruskal-Wallis, followed by Dunn's multiple comparison test (*p<0.05;***p<0.001).

Results - Amylins

Continuous Infusion of Unlipidated SARA and DACRA Agonists Elicit Body Weight Loss and Reduction in Food Intake in DIO Rats

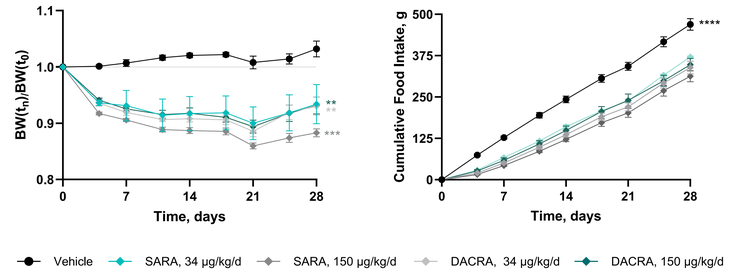


Figure 3. Continuous infusion of SARA and DACRA peptides in DIO SD rats. Left: Percent body weight loss relative to vehicle and Right: Cumulative food intake. DIO rats (n=6/group) on 60% high fat diet were implanted with an Alzet pump filled with a SARA or a DACRA. Peptides were infused at 34 µg/kg/day and 150 µg/kg/day. LC/MS/MS analysis of plasma was performed to quantify and confirm desired peptide concentrations. The maximum achieved BWL of 11–14% relative to vehicle, is comparable to reported Eloralintide and Cagrilintide values [3]. Data shown as mean ± SEM. Data were analyzed using a mixed-effects model, followed by Dunnett's multiple comparisons test (*p<0.05;***p<0.001 ;****p<0.0001).

Conclusions

1. Continuous infusion of unlipidated incretin and amylin peptides produced body weight loss comparable to that of established lipidated peptides.
2. Continuous infusion of unlipidated dual and triple agonists reduced body fat in DIO mice.
3. Lipidation is not required for ultralong-acting anti-obesity peptides when an alternative technology is used, enabling half-life extension beyond albumin binding limits [4].
4. Potent unlipidated peptides can benefit from a technology providing slow, tuned-release, uncoupling the need for the peptide to supply both potency and half-life extension.

References

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Acknowledgments

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Disclosures

All authors are employees of Prolynx Inc. and may hold stock/equity in the company.