A Nature-Derived Peptide Promotes Satiety Hormone Response and Weight Loss In vivo

Marina Abramov, Eden Goldfarb, Dikla Haham, Eyal Akiva*, Jan-Willem Van Klinken, Zohar Barbash
Lembas Bio, 13 Hapardes St., Tel Mond, Israel · *eyal@lembas.bio

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Why recruit the gut's own GLP-1?

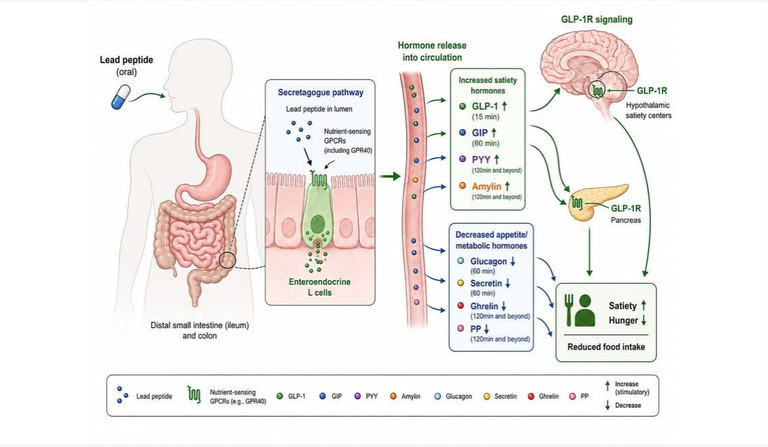
GLP-1 receptor agonists transformed obesity care, but GI intolerance, cost and weight regain after stopping limit persistence. A meal releases GLP-1 through nutrient-sensing GPCRs (GPR40/41/119/120) on intestinal L cells. **Can peptides already present in food proteins engage those same receptors?**

AI-guided mining of the edible proteome

54,576 edible proteins, 440 organisms	**111M** 9–20 aa fragments	**836,606** carry a GG motif	**2,000** AlphaFold-modeled vs 4 GPCRs
46 synthesized & HTRF-screened	**13** to dose-response	**6** dose-responsive secretagogues	**2 leads** NDP-35 · NDP-45

NDP-35 (LEVGNGGMT, *Coffea arabica* α-galactosidase): potent, essentially selective **GPR40 agonist, EC_{50} = 32.7 nM**. **NDP-45** (banana aquaporin): multi-receptor, GPR40 231 nM · GPR41 377 nM.

Proposed mechanism of action



Oral peptide activates nutrient-sensing GPCRs on L cells → ↑ GLP-1, GIP, PYY, amylin; ↓ glucagon, secretin, ghrelin, PP → satiety ↑, food intake ↓.

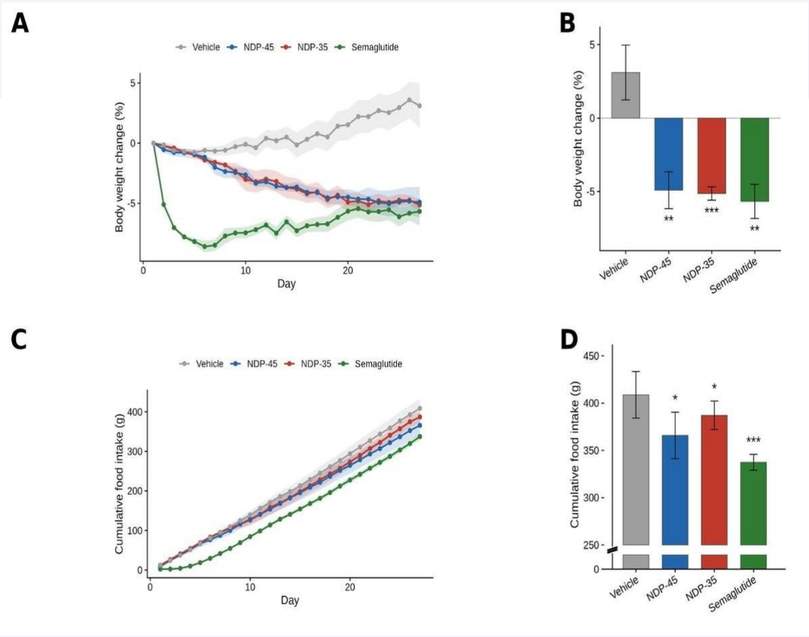
Key finding

An oral peptide found in coffee protein triggers the gut's own satiety hormones and cut body weight ~5% in obese rats in 28 days

vs. a 3% gain on vehicle · endpoint similar in magnitude to a semaglutide reference arm

DIO rats · oral enteric capsules · 28 days

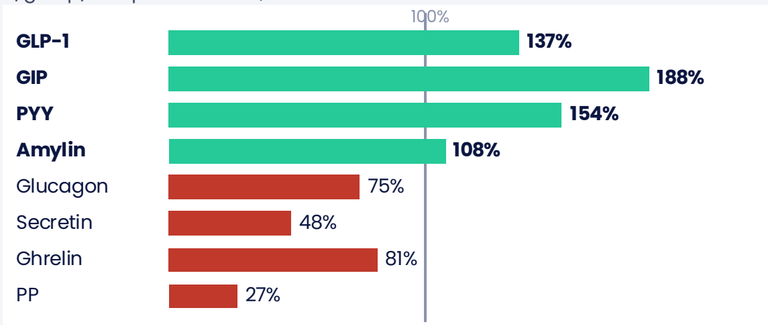
Male DIO Sprague-Dawley rats; NDP-35 or NDP-45 5 mg/kg BID; semaglutide 10 nmol/kg SC QD (reference); n = 6 (NDP-45 n = 5)



(A) Body weight change, (B) endpoint, (C) cumulative food intake, (D) endpoint. *P<0.05, **P<0.01, ***P<0.001 vs vehicle. Lipids, fasting glucose (P = 0.70), liver AST/ALT and organ weights unchanged.

Mice · a meal-like hormone response

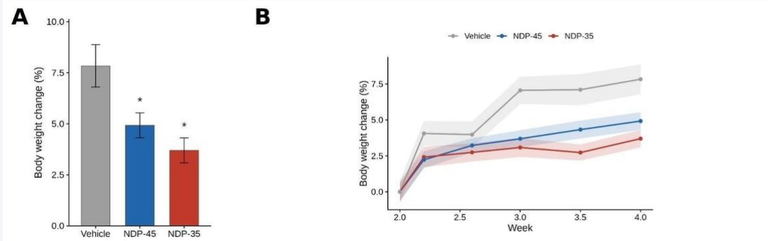
Single intraduodenal dose (10 mg/kg), fasted C57BL/6 mice, n = 5/group/timepoint. NDP-35, % of time-matched vehicle:



■ satiety hormones ↑ ■ appetite/metabolic hormones ↓ (all adj. P<0.05). No acute pro-inflammatory response (TNFα, MCP-1, resistin not elevated).

DIO mice · continuous intraduodenal · 28 d

ALZET pumps; NDP-35 2 mg/kg/d, NDP-45 3 mg/kg/d; n = 6. Lower weight gain (*P<0.05) and food intake vs vehicle.



Safety snapshot · NDP-35

- **Not genotoxic:** Mini-Ames (5 strains, ±S9, ≤1000 µg/well) and CHO-K1 micronucleus (≤5000 µM) negative
- **28-day GLP oral study** (OECD 407, SD rats; 5, 15, 40 mg/kg/d): no treatment-related adverse effects; **NOAEL 40 mg/kg/d**, highest dose tested
- **Digested like food:** intact peptide undetectable after 30 min of simulated intestinal digestion (INFOGEST)
- **In silico:** non-allergenic, non-toxic, non-haemolytic predictions