Title: CagriSema driven weight loss in diet-induced obese rats prevents counter-regulation of weight loss associated reduction in energy expenditure

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Word Count: 250/250 words

Background: CagriSema, a combination of cagrilintide (amylin analogue) and semaglutide (glucagon-like peptide-1), induces weight loss (WL) by suppressing food intake and is under clinical development for obesity and type 2 diabetes treatment. This study assessed if counteracting mechanisms on metabolic adaptation (MA; weight-independent suppression of total energy expenditure [TEE]) are involved in the WL effects of CagriSema.

Methods: Diet-induced obese male rats received daily treatment (2 nmol/kg s.c.) of CagriSema, vehicle-control (VC) or VC weight-matched (WM) to Cagrisema by calorie-restriction for 3-weeks. Food intake and TEE effects of CagriSema were measured.

Results: CagriSema and WM-rats lost ~11% body weight (~16% vehicle-adjusted, n=10-11) and ~50% lower cumulative food intake vs. VC ($p<0.0001$). WM-rats needed 15% fewer calories to induce WL comparable to CagriSema. Mean TEE was ~21% lower in WM-rats vs. VC (2.54±0.10 vs. 3.21±0.10 kcal/h, respectively, $p<0.001$); no TEE difference between CagriSema and VC ($p=0.20$). This suggests TEE reduction in WM-rats was driven by active TEE (MA) downregulation and CagriSema treatment counter-acted this effect. Mono-treatment with cagrilintide and semaglutide also counter-acted the reduction in TEE in WM-rats (~10%, $p<0.01$ vs.VC) with no TEE difference from VC ($P\geq0.73$). Analyses identified 1) plasma triiodothyronine elevated in CagriSema vs. WM-rats, (2) plasma thyroxine decreased in WM not CagriSema-rats, and (3) lower mitochondrial proton leak in WM vs. CagriSema- and VC-rats.

Conclusion: CagriSema prevented MA associated with WL. The underlying mechanisms could involve elevation of triiodothyronine and prevention of thyroxine reduction. Human trials are needed to confirm the counteracting actions of CagriSema on MA.

Conflicts of Interest: Dr. David Attalla, M.D., FRCPC serves as a consultant for ad boards for Bausch, Bayer, Novo Nordisk; as a speaker for Bausch, Bayer, Boehringer Ingelheim, Eisai, Humber River College, Idorsa, Jannssen, Lilly, Novo Nordisk, and as a paid instructor for JFK Neurology Residency, Southlake Hospital. He is self-employed and associated with research work for London Health Sciences and YorkU.

Financial support: Research relating to this abstract was funded by Novo Nordisk A/S.