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☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

Describe how sample size was determined.

Sample sizes were determined on the basis of homogeneity and consistency of characteristics in the selected models and were sufficient to detect statistically significant differences in body weight, food intake and serum parameters between groups, while also ensuring no more animals than necessary were used. These assessments were based on extensive experience with these models and endpoints, where both t-tests and ANOVA statistical tests have been used.

2. Data exclusions

Describe any data exclusions.

No samples or animals were excluded from analyses

3. Replication

Describe whether the experimental findings were reliably reproduced.

All experiments have been replicated successfully and all findings reported have been reliably reproduced.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

Animals were randomized into the treatment groups based on body weight such that the mean body weights of each group were as close to each other as possible, but without using excess number of animals.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

Researchers were not blinded to group allocations

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒	A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	A statement indicating how many times each experiment was replicated
☐	☒	The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒	A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒	The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted
☐	☒	A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒	Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	Prizm v7 for Mac OS X was used for statistical analyses. Biacore T200 evaluation software V.1 was used for data analysis and curve fitting. LabMaster/PhenoMaster TSE lab system software (version 3.1.4) was used to calculate respiratory exchange ratios.

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	Unique materials used in these studies are either available from the commercial sources listed in the manuscript or may be made available to academic researchers for non-commercial use subject to the terms of a mutually agreeable Material Transfer Agreement.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	Primary antibodies used in these studies at the following dilutions were: Goat anti-fos (1:100, Santa Cruz sc-52-G) Rabbit anti-CGRP (1:500, Fisher Scientific NC0538736, T-4032.0050). For c-Fos/GFRAL co-localization: sheep anti-GFRAL (1:200, R&D Systems AF5728) and rabbit monoclonal anti-c-Fos (1:100, CST (clone 9F6) #2250). Anti-GFRAL (AF5728) does not bind to Gfral-related proteins by ELISA (R&D) and fails to stain the Gfral KO brainstem, thus demonstrating its specificity. Fos antibody specificities have been confirmed by numerous groups using chromatin immunoprecipitation (see manufacturers' websites). Rabbit anti-RET (1:200, Cell Signaling Technology 14556). Rabbit anti-pS6 (1:200, Cell Signaling Technology 4858). Rabbit anti-pErk (1:200, Cell Signaling Technology 4370). The Cell Signaling Technology anti-RET rabbit mAb #14556 is well validated by the manufacturer for specific IHC staining in RET-positive tissues and cells. Bhinge et al., used this mAb to demonstrate specific interaction of endogenous RET and EGFR following EGF stimulation (Oncotarget. 2017 Apr 18; 8(16): 27155–27165) The Cell Signaling Technology anti-pS6 rabbit mAb 4858 and anti-pErk1/2 rabbit mAb 4370 are well validated for IHC and shown to be specific for the phosphorylated form of the proteins with loss of staining after phosphatase treatment of cells. These antibodies have been used extensively in the literature (25+ citations for each). Primary antibodies were detected with secondary antibodies labeled with Alexa Fluor 488, Alexa Fluor 594, Cy3, or Alexa Fluor 647 from Jackson ImmunoResearch (catalog numbers: 313-605-046, 115-606-071, 115-546-071, 111-606-046, 111-606-071, 111-585-003) and ThermoFisher Scientific (catalog numbers: A-11016, A-11045, A-27034, A-21448, A-11015, A-21202, A-31571).

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	293T cells were purchased from ATCC (catalog # CRL-3216)
b. Describe the method of cell line authentication used.	The 293T cells used were not authenticated
c. Report whether the cell lines were tested for mycoplasma contamination.	The 293T cells were not tested for mycoplasma contamination
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	N/A

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

C57BL/6 mice were used for GDF15 and cisplatin-induced weight loss studies.
cFOS studies were performed in C57BL/6 mice.
GFRAL KO mice were purchased from Taconic (#TF3754) on a mixed 129/SvEv-C57BL/6 background and backcrossed for 7 generations to >98% C57BL/6 background at NGM's animal facility.
GLP1R KO mice on C57BL/6 background were bred at Merck's animal facility.
Mc4R.K314X mutant rats (FatRat; Mc4R TGEM) were purchased from Taconic.
Leptin Receptor deficient rats (ZF Rat) were purchased from Charles River.
Experiment were performed with animals of a single gender, usually male, but GDF15-induced anorexia and body weight loss studies have been repeated with C57BL/6 female mice.
The weight gain phenotype of GFRAL KO mice on high fat diet has also been confirmed in female mice.
All mouse experiments were conducted in mice ranging from 2 to 6 months of age.
Rat experiments were conducted in animals ranging from 7 to 9 weeks of age.
Animals were housed singly during studies.
All injections and tests were performed during the light cycle.
All animal experiments were conducted with NGM or Merck IACUC approved protocols.
All relevant ethical requirements were complied with throughout these studies.

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

This study did not involve human research participants