

## Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

### Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- |                                     |                                     |                                                                                                                                                                                                                                                            |
|-------------------------------------|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>                                                               |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A description of all covariates tested                                                                                                                                                                                                                     |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons                                                                                                                                        |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | For null hypothesis testing, the test statistic (e.g. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> values as exact values whenever suitable.</i>                            |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings                                                                                                                                                           |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes                                                                                                                                     |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | Estimates of effect sizes (e.g. Cohen's $d$ , Pearson's $r$ ), indicating how they were calculated                                                                                                                                                         |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

### Software and code

Policy information about [availability of computer code](#)

Data collection

Code to run Peptide Predictor is freely available at <https://github.com/Svensson-Lab/pro-hormone-predictor>

Data analysis

All information needed to run the program is detailed in the Methods section and in the code.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

### Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

All raw data have been provided in the manuscript and its supplementary files. There are no restrictions on data availability.

## Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

|                                                                    |                   |
|--------------------------------------------------------------------|-------------------|
| Reporting on sex and gender                                        | No human studies. |
| Reporting on race, ethnicity, or other socially relevant groupings | N/A               |
| Population characteristics                                         | N/A               |
| Recruitment                                                        | N/A               |
| Ethics oversight                                                   | N/A               |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

## Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sample size     | Sample sizes were pre-determined based on power calculations. Animal experiments were performed with an n=3-15 per group based on power calculations and on the number of animals typically used for these procedures in the field.                                                                                                                                                                                                              |
| Data exclusions | No data were excluded.                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Replication     | In vitro experiments include three biological replicates. In vivo acute food intake experiments in mice were reproduced three times with three animals per group. Acute food intake experiments in pigs were reproduced two times with four animals per group. Chronic treatment studies in mice were reproduced twice using separate cohorts of mice. For all experiments in this paper, all attempts to replicate the results were successful. |
| Randomization   | Mice and pigs were randomly assigned to treatment groups for in vivo studies. For in vitro studies, treatment groups were assigned randomly.                                                                                                                                                                                                                                                                                                     |
| Blinding        | Blinding was not performed for animal experiments due to the need to observe possible behavioral effects, and blinding might be unethical. For certain animal experiments, different administration routes or surgeries make blinding impractical or not possible. Blinding was not performed for in vitro experiments due to the objective nature of the assays not likely influenced by observer bias.                                         |

## Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

### Materials & experimental systems

| n/a                                 | Involved in the study                                           |
|-------------------------------------|-----------------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Antibodies                  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Eukaryotic cell lines       |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology          |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Animals and other organisms |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                          |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern           |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Plants                                 |

### Methods

| n/a                                 | Involved in the study                           |
|-------------------------------------|-------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |

## Antibodies

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibodies used | The antibodies used are as follows: rabbit monoclonal CREB (D76D11) (#4820, CST), rabbit monoclonal phospho-CREB (Ser133) (87G3) (#9198, CST), rabbit monoclonal phospho-PKA substrate (RRXS*/T*) (100G7E) (#9624, CST), rabbit monoclonal p44/42 MAPK (Erk1/2) (#9102, CST), rabbit phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) antibody (#9101, CST), and rabbit monoclonal anti-alpha tubulin (#AB4074, Abcam). Mouse monoclonal anti-beta actin AC-15 HRP (#AB49900) was from Abcam. Donkey anti-rabbit IgG (HRP) (#NA934) was from Cytiva (GE). For Fos and Pomc co-immunostaining, the following antibodies were used: Fos antibody (Synaptic Systems, #226 308) and Pomc antibody (Phoenix Pharmaceuticals, #H-029-30).                                                                                                                                                                                    |
| Validation      | Cell Signaling antibodies used have been validated for specificity by the vendor. The Fos and Pomc antibodies have been validated using established positive and negative controls. CREB (D766D11) has specificity for human, mouse, rat, hamster, monkey, drosophila. Phospho-CREB (87G3) has specificity for human, mouse, rat. Phospho-PKA substrate (9624) has specificity for all species. p44/42 MAPK (Erk1/2) Antibody #9102 has specificity for H M R Hm Mk Mi Z B Pg Sc. Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) Antibody #9101 has specificity for H M R Hm Mk Mi Dm Z B Pg Ce. Tubulin antibody (AB4047, Abcam) has specificity for Chinese hamster, Chicken, Cow, Rat, Mouse, Human. Beta-actin (AB49900, Abcam) has reactivity for Mouse, Rat, Hamster, African green monkey, Human, Cow, Dog. Fos antibody (226 308) reacts with mouse, rat, human. Pomc antibody (H-029-30) reacts with mouse. |

## Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

|                                                                      |                                                                                                                                                            |
|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cell line source(s)                                                  | NS-1 rat neuronal cell line (R04-0001-AP, Cellomics)<br>Neuro2a cell line (#CCL-131, ATCC)<br>INS1 832/13 rat insulinoma cell line (#SCC20, Sigma-Aldrich) |
| Authentication                                                       | All cell lines were directly purchased from vendors.                                                                                                       |
| Mycoplasma contamination                                             | All cell lines were negative for mycoplasma.                                                                                                               |
| Commonly misidentified lines<br>(See <a href="#">ICLAC</a> register) | No commonly misidentified cell lines were used.                                                                                                            |

## Animals and other research organisms

Policy information about [studies involving animals; ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

|                         |                                                                                                                        |
|-------------------------|------------------------------------------------------------------------------------------------------------------------|
| Laboratory animals      | 6-20 week old C57BL/6 mice (Jackson labs) and 3-4 month old Yucatan minipigs (S&S Farms, CA) were used.                |
| Wild animals            | No wild animals were used.                                                                                             |
| Reporting on sex        | Sex was considered in the study design. The use of male or female animals is stated in the results and figure legends. |
| Field-collected samples | No field work.                                                                                                         |
| Ethics oversight        | All animal work was approved by animal ethics committee #34270 and #32982.                                             |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Plants

|                       |                     |
|-----------------------|---------------------|
| Seed stocks           | No seed stocks.     |
| Novel plant genotypes | No plant genotypes. |
| Authentication        | N/A.                |