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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	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	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)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	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	Oxygen consumption, carbon dioxide production and food intake were recorded using the Promethion core system (Sable Systems International) with data processing using OneClickMacroV2.52.1 and Macrointerpretersetup_v2_47 or the Phenomaster Home Cage System (TSE Systems) with PhenoMaster software v.8.2.9. Continuous body temperature and motor activity were measured with G2 E-Mitter telemetric devices (Starr Life Sciences) or with RFID temperature transponders (UCT-2112 microchips, Unified Information Devices). E-mitter data was recorded by placing ER4000 Receivers under the cages within the TSE cabinet. Temperature data was integrated in the Phenomaster software. RFID temperature transponder data was recorded by using UID Mouse Matrix system (Unified Information Devices) in combination with the Sable system.
Data analysis	Statistical analyses were performed using GraphPad Prism v.9.5.1 or SPSS v.29.0.2.0 (IBM). The source code used to analyze the snRNA-seq and produce figures is available at https://github.com/perslab/Sass-2024/. All analyses were performed in Rstudio (2022.07.2+576) with R (4.1.3). Data were loaded and manipulated using data.table (1.14.2) and tidyverse (1.3.1). Linkage disequilibrium (LD) operations were performed using plink1.975, ggLD (https://github.com/mmkim1210/ggLD), and LDLink77. All results can be reproduced by following the code available. in: https://github.com/MarioGuCBMR/nk2r_hk1_genetics. Specific statistical tests were described in relevant figures, figure legends, or supplemental material.

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

We have included the following Data Availability statement in the methods section of the manuscript:
snRNA-seq data are deposited to the NCBI Gene Expression Omnibus under accession number: GSE276735. Source data for all studies presented are provided with this paper.

I can confirm that there are no data generated and included in this paper that are restricted.

We have also included analysis of previously published human genetic cohorts:
1. https://www.sdu.dk/da/sif/rapporter/2011/inuit_health_in_transition
2.https://www.sdu.dk/da/sif/rapporter/2019/befolkningsundersoegelsen_i_groenland
3. Bjerregaard, P. et al. Inuit health in Greenland: a population survey of life style and disease in Greenland and among Inuit living in Denmark. Int. J. Circumpolar Health 62 Suppl 1, 3–79 (2003).
4. T2D Knowledge Portal (http://t2d.hugeamp.org) was used for analyzing HbA1c associations.
5. Open Target Genetics (OTG) were utilized to query the variant-to-gene (V2G) scores used for gene prioritization and the associations of causal variants with expression quantitative trait loci (eQTLs).

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	n/a
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

Life sciences study design

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

Sample size	No statistical methods were applied to predetermine sample size for in vivo pharmacology experiments. Sample sizes were determined based on previous experience with related experimental setups (PMID: 34048700).
Data exclusions	For continuous body temperature measurements in mice, four E-mitters malfunctioned after implantation and measurements of these mice were excluded from analysis. During the s.c. vs ICV crossover study, two mice had to be sacrificed due to health concerns related to the surgeries. In the NHP study, some measurements for the blood parameters failed and couldn't be repeated due to limited or no remaining sample.
Replication	To ensure reproducibility and replication of our core findings, animals studies were independently and successfully repeated by four researchers (FS, JPE, JBH, TM) independently as well as a third party, contract research organization (Gubra) and comparable effect sizes were observed/confirmed.
Randomization	Mice were grouped based on body weight, such that each group had the same average body weight upon study start. Randomization for

Randomization	nonhuman primates was not applicable as all animals received increasing doses of compound and then a monitored period of drug washout.
Blinding	The mouse studies were not blinded to the investigators but were conducted according to standardized protocols and procedures. The NHP study was not blinded to investigators as all animals received dose escalation and wash-out of the NK2R agonist compound. This is common practice for safety and dose-finding studies.

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
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	FOS (Cell Signalling, 2250), GFP (Aves Laboratories, 1020), AKT (Cell Signaling, 9272), pAKT T308 (Cell Signalling, 9275), Tyrosine hydroxylase (Abcam, ab137869), UCP1 (Abcam, ab10983), Alexa Fluor 488 and 568 secondary antibody (Invitrogen, A-11039, A-11011), Anti-rabbit IgG secondary (Jackson Immuno Research, 111-035-144, 1:5000)
Validation	All antibodies have been validated for use in western blotting in mice. Validation statements from the websites of the antibody companies include: FOS - This antibody detects endogenous levels of total c-Fos protein. The antibody does not cross-react with other Fos proteins, including FosB, FRA1 and FRA2. c-Fos (9F6) Rabbit mAb #2250 non-specifically stains fixed frozen mouse spleen and liver by immunofluorescence (Nakabeppu, Y. and Nathans, D. (1991) Cell 64, 751-9.) GFP - This antibody was validated by western blot analysis (1:5000 dilution) and immunohistochemistry (1:500 dilution) using transgenic mice expressing the GFP gene product. AKT - The Akt Antibody detects endogenous levels of total Akt1, Akt2 and Akt3 proteins. The antibody does not cross-react with related kinases (e.g. Cross, D.A. et al. (1995) Nature 378, 785-9.) pAKT T308 - Phospho-Akt (Thr308) Antibody detects endogenous levels of Akt only when phosphorylated at Thr308 (e.g. Cross, D.A. et al. (1995) Nature 378, 785-9.) Tyrosine hydroxylase - Monoclonal antibody made using Abcam hybridoma-based technology and validated at 1/500 concentrations for western blotting (PMID: 37179330) UCP1 - Synthetic Peptide within Human UCP1 aa 100-200 conjugated to Keyhole Limpet Haemocyanin (PMID: 35675775) For Secondary antibodies: For FOS (Cell Signalling, 2250, 1:1000) and GFP (Aves Laboratories, 1020, 1:1000), we used a secondary antibody conjugated to Alexa Fluor 488 and 568 (Invitrogen, A-11039 (anti-chicken IgG), A-11011 (anti-rabbit IgG), 1:250) For AKT (Cell Signaling, 9272, 1:1000), pAKT T308 (Cell Signalling, 9275, 1:1000), Tyrosine hydroxylase (Abcam, ab137869, 1:1000), UCP1 (Abcam, ab10983, 1:7500), we used peroxidase-conjugated AffiniPure™ Goat Anti-Rabbit IgG (H+L) (Jackson Immuno Research, 111-035-144, 1:5000)

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	COS-7 cells were purchased from ATCC.
Authentication	Cell lines were not authenticated
Mycoplasma contamination	Cell line was routinely tested for mycoplasma contamination and found to be negative for mycoplasma contamination.

Commonly misidentified lines (See ICLAC 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	C57Bl/6NRj (WT) mice, B6.V-Lepob/JRj (ob/ob) mice and RjOrl:SWISS (CD-1®) mice were purchased from Janvier Labs (Le Genest-Saint-Isle, France). B6.129S4-Mc4rtm1Lowl/J (Mc4r KO), Ccktm1.1(cre)Zjh/J, B6.129-Leprtm3(cre)Mgmj/J, Calcrtm1.1(cre)Mgmj/J, B6;129-Gt(ROSA)26Sortm5(CAG-Sun1/sfGFP)Nat/J and Gt(ROSA)26Sortm1(CAG-EGFP/Rpl10)Dolsn mice were purchased from the Jackson Laboratory (Maine, US). The Ucp1 KO line was kindly provided by Prof. Karsten Kristiansen (University of Copenhagen). Nk2r conditional KO mice and B6N-Tacr2tm1Zpg (Nk2r floxed) mice, were generated by GenOway (Lyon, FR). These mice were also used in the studies where AAV-Cre and AAV-GFP viruses were injected into the DVC to generate NK2R-DVC-Cre and NK2R-DVC-GFP mice, respectively. Adult male and female mice aged 12-30 weeks were used for all studies. For the nonhuman primate study, the mean ages of the rhesus macaques at study start were 20.6 years old (standard deviation=2.1) for females and 15.4 years old (standard deviation=4.3) for males.
Wild animals	Study did not involve wild animals.
Reporting on sex	Murine findings are reported for male and female mice as indicated in results, figures, figure legends and methods. NHP data are reported for both male and female macaques. Human genetic analysis includes both males and females.
Field-collected samples	Study did not involve samples collected from the field.
Ethics oversight	All mouse studies were approved by The Danish Animal Experiments Inspectorate (permit number: 2018-15-0201-01441 and 2023-15-0201-01386) and the University of Copenhagen (project number: P20-015, P22-209). Animal experiments performed at the University of Michigan were approved by the University of Michigan Committee on the Use and Care of Animals (Protocol#00011066) and in accordance with Association for the Assessment and Approval of Laboratory Animal Care and National Institutes of Health guidelines. The nonhuman primate studies were conducted in compliance with all federal regulations, including the United States Animal Welfare Act. Studies were reviewed and approved by the OHSU/ONPRC Institutional Animal Care and Use Committee. The ONPRC is accredited by AAALAC International.

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