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Reporting Summary

Nature Research 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 Research policies, see <u>Authors & Referees</u> and the <u>Editorial Policy Checklist</u>.

Statistics		
For all statistical analys	ses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.	
n/a Confirmed		
☐ ☐ The exact sam	nple size (n) for each experimental group/condition, given as a discrete number and unit of measurement	
A statement of	on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly	
The statistical Only common t	test(s) used AND whether they are one- or two-sided ests 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 descript AND variation	tion of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) in (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)	
For null hypot	thesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted is exact values whenever suitable.	
For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings		
For hierarchic	cal and complex designs, identification of the appropriate level for tests and full reporting of outcomes	
Estimates of e	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 o	code	
Policy information abo	ut availability of computer code	
Data collection	Prism, Excel	
Data analysis	Prism, Excel	
For manuscripts utilizing cust	om algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.	
Data		
 Accession codes, un A list of figures that 	ut availability of data include a data availability statement. This statement should provide the following information, where applicable: sique identifiers, or web links for publicly available datasets have associated raw data restrictions on data availability	
Source data for all figure	s are provided with the paper. All other data supporting the findings of this study are available from the authors upon request.	
Field-speci	ific reporting	
Please select the one b	pelow 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 d	ocument 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 Sample size was chosen based on prior experience of the investigators with similar experiments previously published. The authors have published numerous peer reviewed papers demonstrating clear positive findings with similar sample sizes for the types of experiments included. Data exclusions No data points were excluded from analysis in any experiment depicted in this manuscript. Replication The experimental findings were reliably reproduced in several independent experiments. Randomization Randomization was performed by blinding the investigator to genotype and allowing them to choose each subject blindly. No animals or slices were excluded from the analysis. Randomization was performed by blinding the investigator to genotype and allowing Blinding

them to choose each subject blindly. For studies using pharmacological agents, the investigator was aware of the agent being used, but was not aware of the genotypes of the animals used. Investigators were not aware of the specific group to which an animal was assigned when

doing the experiment or analysis until after completion.

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 Methods	
n/a Involved in the study Antibodies	n/a Involved in the study ChIP-seq	
Eukaryotic cell lines Palaeontology	Flow cytometry MRI-based neuroimaging	
Animals and other organis Human research participal Clinical data		
Antibodies		
L P C	Antibodies JCP1 Abcam ab10983 PGC1alpha Abcam ab54481 Ekmt2 Abcamab55963 Beta-arrestin-1/2 antibody (rabbit polyclonal); Provided by Dr. Vsevolod Gurevich Deta-Actin Cell Signaling 4970S	
Validation A	Antibodies were validated by the manufactureres of by Dr. Vsevolod Gurevich.	
Eukaryotic cell lines		
Policy information about cell line	5	
Cell line source(s)	HEK 293T cells (ATCC, American Type Culture Collection, CRL-3216); 3T3-F442A pre-adipocytes (Kerafast)	
Authentication	Quality Control by ATCC and Kerafast	
Mycoplasma contamination	All cell lines tested negative for mycoplasma contamination.	
Commonly misidentified lines (See <u>ICLAC</u> register)	n/a	
Animals and other or	ganisms	

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals Male mice (C57BL6 background) Wild animals

n/a

Field-collected samples

na/a

Ethics oversight

All animal studies were approved by the NIDDK Institutional Animal Care and Use Committee.

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