nature research

Corresponding author(s): Dr. Gerald I. Shulman

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 Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection.
Data analysis	Microsoft Excel for Mac 2011, version 14.1.0, and Graphpad Prism 7 for Mac OS X were used to perform the data analyses and statistical analyses for this study.

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/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

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

Sample size	Sample sizes of n=5-8 for in vivo studies were selected to selected to detect moderate to large (>20%) differences. Significance of differences in data was determined by two-tailed Student's t-test or by ANOVA as necessary (and indicated in the figure legends).
Data exclusions	For studies using the rat model of type 2 diabetes induced in SD rats by high fat diet for four weeks, and treatment with nicotinamide (80 mg/kg) and streptozotocin (45 mg/kg), data from rats with overnight fasted plasma glucose concentrations >300 mg/dL or plasma insulin <20 microU/mL, indicating type 1 diabetes, were excluded from analysis.
Replication	Experiments were repeated more than once and all findings were reproduced. Measurements of the same parameters (eg. EGP, plasma metabolites, etc.) were performed in several different models and treatment conditions, and all data was successfully reproduced.
Randomization	Allocation of organisms to experimental groups was random prior to treatment and data collection. At the beginning of studies, animals were selected to match approximate weight. Upon commencing the studies, animals randomly allotted to the respective groups were then treated accordingly (with drug, diet, etc.) and then studied.
Blinding	Investigators were not blinded during the studies for either group allocation, data collection or analysis. All GC-MS and LC-MS/MS analyses in this manuscript were performed in a blinded fashion.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants

Methods

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

Antibodies

Antibodies used	Primary Antibodies used to determine protein expression were: PEPCK-C H-300 (Santa Cruz Biotechnology, Cat. No.: sc-32879), PCB H-2 (Santa Cruz Biotechnology, Cat. No.: sc-271493), Phospho-CREB Ser133 87G3 (Cell Signaling, Cat. No.: 9198), CREB 48H2 (Cell Signaling, Cat. No.: 9197), Phospho-AMPKα Thr172 40H9 (Cell Signaling, Cat. No.: 2535), AMPKα (Cell Signaling, Cat. No.: 2532), GAPDH D16H11 XP® (Cell Signaling, Cat. No.: 5174), G6Pase (Santa Cruz Biotechnology, Cat. No.: sc-27198), Phospho-ACC (Cell Signaling, Cat. No.: 3661), and ACC (Cell Signaling, Cat. No.: 3676). Secondary antibodies used were: Goat Anti-Rabbit IgG Antibody, F(ab')2, HRP conjugate (Cat. No.: AQ132P EMD Millipore), Anti-Mouse IgG (Fab specific)–Peroxidase antibody produced in goat (Cat. No.: A3682 Sigma) and Rabbit Anti-Goat IgG Antibody, HRP conjugate (Millipore Cat. No.: AP106P)
Validation	All antibodies were previously validated using cell lysates and rat liver lysates in our lab, and have also been validated by the supplier (Santa Cruz Biotechnology states that "primary antibodies directed to mammalian target proteins have been characterized for reactivity against mouse, rat and human proteins ... [and] are recommended for use in most assays including Western blot, immunoprecipitation, immunostaining, and flow cytometry."; Cell Signaling provides clear indication for each antibody as to the specificity, reactivity and recommended application in the antibody datasheet. All antibodies were used only as recommended by the supplier.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Primary hepatocytes isolated from rat livers were used, but no established cell lines were used in this study.
Authentication	Primary hepatocytes studied were determined viable if glucose production in response to pyruvate substrate was observed, and if the general cell morphology was intact. Cells were only plated if the preparation was at least 90% viable (less than 10% cell death).
Mycoplasma contamination	Cell preparations were not tested.
Commonly misidentified lines (See ICLAC register)	N/A

Animals and other organisms

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

Laboratory animals	Male Sprague-Dawley and Zucker Diabetic Fatty rats were acquired from Charles River. All animal studies included rats aged 9-12 weeks that weighed 300-450 g at the time of study, except the portal vein studies where rats weighed 400-600 g. Whole-body ACC1/2 double knock-in mice were a kind gift from Dr. Gregory R. Steinberg, McMaster University and Bruce Kemp, University of Melbourne. All ACC1/2 double knock-in mice used were male and weighed 22-27 g.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected in the field.

Human research participants

Policy information about studies involving human research participants

Population characteristics	The human metformin acute pharmacokinetic study was reviewed and approved by the Yale Human Investigation Committee and written informed consent was obtained from each participant after explanation of the purpose, nature, and potential complications of the study. Plasma metformin concentrations were measured every 10 min in three type 2 diabetic subjects following a single oral 1 g dose of metformin, and in one type 2 diabetic subject taking chronic metformin treatment (1g p.o. twice a day). Plasma metformin concentrations were measured by LC-tandem mass spectrometry as previously described (16).
Recruitment	Patients with type 2 diabetes were recruited from the local community by poster advertisement.