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Corresponding author(s): Dong Kong, PhD

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Life Sciences Reporting Summary

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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.

For all animal experiments, the number of independent mice used is listed in the figure legends. In this study, all control and experimental genotypes were independently replicated for at least 3 times. The chosen sample size in all experiments satisfied the resource equation, where the error of degrees of freedom in t-test or the denominator of F in the ANOVA was between 10 – 20.

2. Data exclusions

Describe any data exclusions.

As stated in the methods section under 'Stereotaxic surgery', all stereotaxic injection sites were verified under electrophysiological microscopy (for electrophysiology-related studies) or by immunohistochemistry (for anatomy and in vivo studies). All 'missed' or 'partial-hit' animals were excluded from data analyses.
For the experiment in figure 3b, silent neurons (which showed no depolarization before diazoxide apply) were excluded from data analyses.

3. Replication

Describe whether the experimental findings were reliably reproduced.

All experimental findings were reliably reproduced.

4. Randomization

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

For data analyses, all animals of the same sex were independently housed and randomly assigned to either experimental or control groups.

5. Blinding

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

Due to the nature of stereotaxic injection and analysis of viral hits (including 'missed' injections or 'incomplete' hits which were later excluded after post hoc analysis of mCherry or GFP expression), all measurements were randomized and blind to the experimenter.

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.	Offline data analysis for electrophysiology was performed by using previously published custom scripts written in Igor Pro 6 (Wavemetrics) and MATLAB (MathWorks). Statistical analyses were performed using GraphPad PRISM 6 software (GraphPad). Imaging data analysis was performed using ImageJ (NIH).

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.	There is no restriction on material availability. We include a statement on data availability in our manuscript, as required by Nature policy.

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 for immunohistochemistry studies include: rabbit anti-DsRed polyclonal (Clontech, 1:2000, Cat#632496, Lot#1612022), chicken anti-mCherry polyclonal (EnCor Biotechnology, 1:2000, #CPCA-mCherry, Lot#6695), chicken anti-GFP polyclonal (Aves Labs, 1:2000, GFP-1010, Lot#GFP697986), rabbit anti-hrGFP polyclonal (Agilent Technologies, 1:1000, Cat# 240142), goat anti-Fos polyclonal (Santa Cruz Biotechnology, 1:150, Cat# sc-52-g, Lot#I0215), rabbit anti-pSTAT3 polyclonal (Cell Signaling Technology, 1:1000, Cat# 9145S, Lot#31), rabbit phosphor-S6 ribosomal protein polyclonal (S235/236) (Cell Signaling Technology, 1:1000, Cat# 4858, Lot#11).

Secondary antibodies include: Alexa594 donkey anti-rabbit IgG (Invitrogen, 1:200, Cat#A-21207, Lot#1890862), Alexa594 donkey anti-chicken IgG (Jackson ImmunoResearch, 1:200, Code#703-585-155, Lot#131340), Alexa488 donkey anti-chicken IgG (Jackson ImmunoResearch, 1:200, Code#703-545-155, Lot#130357), Alexa488 donkey anti-rabbit IgG (Invitrogen, 1:200, Cat#A-21206, Lot#1874771), Alexa488 donkey anti-goat IgG (Invitrogen, 1:200, Cat#A-11055, Lot#1869589).

All antibodies above are in common use or have been validated in other literature for use in mouse. We also confirmed that each antibody stained in an expected cellular pattern and brain-wide distributions at its target proteins. Controls without AAV injections thus no expression of reporter fluorescent proteins, or absence of signals following a gene ablation were also used for validation. We provide detailed catalogue number, source, and dilution for each antibody used in the current study.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

Neuro-2a cell(ATCC® CCL¬131™).

b. Describe the method of cell line authentication used.

The cell lines was authenticated in the lab of origin.

c. Report whether the cell lines were tested for mycoplasma contamination.

The cell line was was tested by using PCR detection kit (ATCC® 30-1012K™).

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.

Not Applicable

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.

Agrp-IRES-Cre (Jax Stock No: 012899), Npy-hrGFP (Jax Stock No: 006417), Pomc-hrGFP (Jax Stock No: 006421), Pomc-Cre (Jax Stock No: 010714), Vgat-IRES-Cre (Jax Stock No: 016962) were previously generated at the BNORC transgenic core and are available at the Jackson Laboratory. Rosa26-LSL-Cas9-GFP (Jax Stock No: 024857) knock-in mice, NOD (Jax Stock No: 001976) mice, Lepr db/db (Jax Stock No: 000642) mice, C57BL/6 (Jax Stock No: 000664) mice were obtained from the Jackson Laboratory. 4-8 week old male mice of every mouse line were used for all experiments, and 4-8 week old female mice were used for clinically relevant experiments, particularly with the Agrp-IRES-Cre and NOD mouse lines. Following stereotaxic injection to express AAVs, mice were individually housed with ad libitum access to regular chow diet and water. Littermates of the same sex were randomly assigned to either experimental or control groups. All experiments with animals were performed in accordance with national and international guidelines and were approved by the Tufts University / Tufts Medical Center Institutional Animal Care and Use Committee (IACUC), in accordance with NIH guidelines.

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.

The study did not involve human research participants.