

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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☒ | ☐ | 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | 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 Leica Application Suite X (LAS X) Version 2.0 , PatchMaster v2x90.5, ScreenWorks 4.0, ZEN software(version 2), EPU

Data analysis GraphPad Prism8, ChemDraw 20.0, Relion 5.0, CryoSparc 4.6, ChimeraX 1.10, coot 0.94, PyMOL 3.04, MotionCor2, Ctffind 4.0

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](#)

The data from this study, along with material from custom products, can be obtained from the corresponding authors upon request. All raw data and statistical analyses are provided in the source data file.

EMDB (Electron Microscopy Data Bank) under accession code EMD-72405 (DAB/Ca2+ consensus), EMD-72407 (DAB/Ca2+ subunit), EMD-72406 (DAB/EGTA)

consensus) and the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCS-PDB) under accession code 9Y2A (DAB/Ca²⁺ consensus), 9Y2C (DAB/Ca²⁺ subunit), 9Y2B (DAB/EGTA consensus).

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](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	From our experience and related studies, 5 cell replicates are sufficient for electrophysiological comparison.
Data exclusions	No data were excluded.
Replication	All electrophysiology data sets were pooled from at least two independent experiments and all results were successfully replicated.
Randomization	Randomization is not relevant to electrophysiology.
Blinding	Blinding was deemed unnecessary for the in vitro functional studies, as these experiments do not involve subjective interpretation of the data by the researchers.

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	Anti-TRPM4 (2040250, Alomone labs, 1:100), Anti-CK-18 (3678929, Bioss, 1:200), Alexa Fluor 555 goat anti-mouse (1500655, Cell Signaling Technology, 1:1,000), Alexa Fluor 488 goat anti-rabbit (3067986, Cell Signaling Technology, 1:1,000).
Validation	The commercially available antibodies were validated by the company.

Eukaryotic cell lines

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

Cell line source(s)	HEK293 cells were purchased from ATCC. HT-29 cells were purchased from the Chinese Academy of Medical Sciences.
Authentication	No further authentication was performed for cell lines used in this study.
Mycoplasma contamination	No mycoplasma testing was performed specifically for this study, the cell lines had been tested negative in the past.
Commonly misidentified lines (See ICLAC register)	HEK cells and HT-29 cells are listed in the register; however, our cell lines come from reliable source and are the only secondary cell type used in this study, which minimizes the risk of any cross-contamination.

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	Both male and female C57BL/6J mice (8 weeks, 20-22 g) were purchased from the Animal Core Facility of Nanjing Medical University. Villin-Cre (Vil1-Cre) mice were purchased from The Jackson Laboratory. Global TRPM4 knockout (Trpm4 ^{-/-}) and Trpm4 ^{flox/flox} mice were obtained from GemPharmatech Co., Ltd.. Mice were kept in individual ventilation cage in an SPF animal facility under a 12/12h light–dark cycle at 23 ± 2 °C with ad libitum access to food and water. All animal experiments were carried out in concordance with the National Institutes of Health Guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978) and approved by the Institutional Animal Care and Use Committee of China Pharmaceutical University (#SYXK 2021-0011, approved for Jan 25th, 2021 to Jan 24st, 2026).
Wild animals	No wild animals were used in this study.
Reporting on sex	Sex is not predetermined in this study, not relevant to any conclusion and not involved in experimental design.
Field-collected samples	No field collected samples were used in this study.
Ethics oversight	All animal care and experimental procedures were carried out in accordance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) approved by the China Pharmaceutical University Institutional Animal Care and Use Committee (#SYXK 2021-0011, approved for Jan 25th, 2021 to Jan 24st, 2026).

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

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A