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Genetically targeted magnetic control of the nervous system

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Change history

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In the version of this article initially published online, first, a relevant citation was omitted. To correct this, the sixth sentence of the introduction, which originally read "one study employed nonthermal magnetogenetic control of somatic tissues to regulate blood glucose[11], but a genetically encoded, single-component magnetogenetic system has yet to be applied to the nervous system," has been rewritten to say "one study employed nonthermal magnetogenetic control of somatic tissues to regulate blood glucose[11] and another utilized a naturally occurring iron-containing magnetoreceptor to trigger neuronal activity[48], but a genetically encoded, single-component magnetogenetic system has yet to be applied to the nervous system of behaving vertebrates." Ref. 48 is provided as follows: Long, X., Ye, J., Zhao, D. & Zhang, S.J. Magnetogenetics: remote non-invasive magnetic activation of neuronal activity with a magnetoreceptor. *Sci. Bull. (Beijing)* **60**, 2107–2119 (2015). Second, the author contribution statement incorrectly listed M.P.B as having performed experiments. This has been corrected to say that M.P.B. provided conceptual help during the development of the prototype channel. Finally, the reporter construct in the right panel of Figure 2e was mislabeled *Camk2a::Cre-EGFP*. This control construct should have been labeled *Camk2a::EGFP*. The errors have been corrected for the print, PDF and HTML versions of this article.

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Contributions

M.A.W. and A.D.G. designed the study. M.A.W., C.J.S., M.O., B.S.B., A.M.P., R.M.G., R.P.G. and A.J.S. performed the experiments. M.A.W., C.J.S., M.O., B.S.B., A.M.P., R.M.G., M.K.P., C.D.D. and A.D.G. analyzed the data. M.P.B. provided conceptual help during the development of the prototype channel. S.K., M.K.P., C.D.D. and A.D.G. supervised the research. M.A.W. and A.D.G. wrote the manuscript with input from coauthors.

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Ethics declarations

Competing interests

The authors declare no competing financial interests.

Integrated supplementary information

Supplementary Figure 1 Model of magnetic activation via Magneto.

(**a**) The cation channel, TRPV4, is gated by stretch (among other diverse classes of stimuli), to depolarize cells. For simplicity, only two of the four homomeric subunits are shown. (**b**) Coupling ferritin to the TRPV4 C-terminus converts TRPV4 to a magnetic field detector. Gating properties were extrapolated from published descriptions of TRPV1 and TRPA1 gating mechanisms[48-50].

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Supplementary Figure 2 Measurement of electromagnet strength over distance.

Empirical determination of the strength of several electromagnets over distance powered by an identical current. Dashed line represents distance between HEK cells and electromagnet during calcium imaging assays. A 3 cm diameter magnet was used for all calcium imaging assays. Δx represents distance between magnet and cells used in calcium imaging.

Source data

Supplementary Figure 3 *In vitro* calcium imaging using Magneto1.0.

(**a**) Mammalian expression vector schematic of Magneto1.0. (**b-g**) Representative images of HEK293 cells used for *in vitro* magnetic stimulation Fluo-4 calcium imaging. (**h**) Quantification of relative calcium fluorescence in response to magnetic stimulation of mCherry+ cells. Replicates are shown as individual coverslips equaling n=6 (TRPV4/ferritin), n=8 (Magneto1.0), and n=6 (Magneto1.0+RR). Total cells analyzed for each condition are n=545 (TRPV4/ferritin), n=565 (Magneto1.0), and n=437 (Magneto1.0+RR). One-way ANOVA, Bonferroni post-test, ($F_{2,17}$=7.509, p=0.0046). (**i**) Representative images of temporal association between calcium fluorescence and magnetic field pulses in an individual Magneto1.0-expressing cell (arrow). Field was pulsed for alternating 10 second periods of on/off. *p<0.05. Data are shown as mean±SEM.

Source data

Supplementary Figure 4 Optimization of Magneto1.0 by improving cellular trafficking.

(**a-e**) HEK293 cells transfected with mCherry-fused variants of Magneto1.0 with combinations of various inwardly rectifying K+ channel 2.1 (Kir2.1) trafficking signals. (**a**) Magneto1.0-mCherry shows diffuse cellular localization, poor membrane expression, and poor transfection efficiency. (**b**) Addition of ER export signal from Kir2.1 to C-terminus of Magneto1.0-mCherry peptide partially improves Magneto expression. (**c**) Addition of Kir2.1 membrane trafficking signal (TS) significantly improves membrane expression of Magneto. (**d**) Dual addition of membrane trafficking and ER export signals improves expression relative to Magneto1.0 but not relative to a single membrane trafficking signal. (**e**) Tandem Kir2.1 membrane trafficking/ER export signals on Magneto1.0 C-terminus improves expression but not relative to **c**. n=2 coverslips and >100 cells analyzed per trafficking modification examined.

Supplementary Figure 5 Viability of Magneto2.0-transfected mammalian cells.

(**a-d**) Viability of Magneto2.0 transfected HEK293 cells several days post transfection (DPT). Images show bright field and mCherry fluorescence. Zoom increased in (**c-d**) to increase single cell resolution following significant cell division. Images are representative of n>100 cells examined.

Supplementary Figure 6 Calcium imaging controls using thapsigargin.

(**a**) Graph of Fluo-4 fluorescence using HEK293 cells transfected with *Magneto2.0-p2A-mCherry* and treated with thapsigargin over a period of 60 minutes. Arrow indicates addition of 1 μM thapsigargin to the imaging chamber after a 30 second baseline recording of calcium fluorescence. Dashed box indicates analysis window for “thapsigargin” experiments in panel **b**. n=114 cells analyzed from 3 independent replicates. (**b**) Time course showing the magnetic activation of Magneto2.0 expressing cells in the presence and absence of thapsigargin. All cells from one replicate shown per condition, n=102 cells (Magnet) and n=52 cells (Thapsigargin). In the “thapsigargin” condition, cells were pre-treated with 1μM

thapsigargin and calcium imaging was initiated 30 minutes post-thapsigargin treatment during the window (dashed box) shown in panel **a**. (**c**) Quantification of maximal calcium fluorescence of HEK293 cells expressing Magneto2.0 and subjected to the above conditions using Fluo-4 calcium imaging 24 hours post-transfection. Values shown are the average maximal Fluo-4 fluorescence values per cell relative to baseline for each condition. Data points are shown as total cell averages among individual coverslips. n=114 (Thapsigargin) and n=396 (Magnet) cells analyzed from n=3 (Thapsigargin) and n=5 (Magnet) independent replicates. Welch's two-tailed unpaired t-test, ($t_{2.882}$=4.457, p=0.0395). "Magnet" data are duplicated from Figure 1. *p<0.05. Data shown as mean±SEM.

Source data

Supplementary Figure 7 Control analyses for electrophysiological characterization of Magneto2.0.

(**a**) Representative trace showing that injection of depolarizing current evokes spikes in doubly transduced EGFP+ Magneto2.0 expressing neurons. (**b**) No change in AP latency between conditions of current injection or magnetic field application in transduced neurons (measured from time immediately preceding depolarization). Unpaired two-tailed t-test, (t_{22}=1.628, p=0.1178) (threshold), (t_{22}=1.676, p=0.1079) (peak). (**c-g**) Membrane properties are unchanged under conditions of either current injection or magnetic stimulation in hippocampal neurons doubly transduced with *CMV::DIO-Magneto2.0* and *CaMKIIα::Cre-EGFP*. Unpaired two-tailed t-test, (t_{22}=0.1926, p=0.8498) in **c**, (t_{22}=1.335, p=0.1954) in **d**, (t_{22}=0.1290, p=0.8985) in **e**, (t_{22}=1.052, p=0.3042) in **f**, (t_{22}=0.4086, p=0.6868) in **g**. (**h**) Injection of depolarizing current evokes APs in Cre-negative *DIO-Magneto2.0* transduced EGFP+ neurons. n=12 neurons analyzed for each condition shown in (**b-g**). ns: not significant. Data shown as mean±SEM.

Source data

Supplementary Figure 8 Controls for magnetic stimulation in brain slice electrophysiology.

(**a**) Paired traces depicting the onset of action potentials following

current injection (black) and magnetic stimulation (red) for the same neuron co-transduced with AAVs carrying *CaMKIIα::Cre-EGFP* and *CMV::DIO-Magneto2.0*. Overlay shows a modest delay of action potential onset (50-100 ms) when neurons are stimulated with static magnetic fields. (**b**) Magnified traces of the resting state from three additional neurons co-transduced with the above viruses. Neurons are shown immediately prior to action potential initiation as static magnetic fields are brought more closely to the cells using a micromanipulator, a process requiring roughly 1 second. Traces do not show interference coming from ~50 mT static magnetic fields in close proximity to the recording apparatus.

Source data

Supplementary Figure 9 Application of Magneto1.0 to zebrafish behavior *in vivo*.

(**a**) Schematic of *trans cardiac myosin light chain 2 (cmcl2)::GFP* element and its expression in 24 hpf zebrafish embryos for positive transgenic selection. n>100 fish examined. (**b**) Schematic of Magneto1.0 construct used: Tol2: Tol2 transposon sites; ß-Actin: promoter; IRES: internal ribosomal entry site; nls-EGFP: nuclear localized enhanced GFP. (**c**) Quantification of the number of coils in WT (uninjected) and *ß-actin::Magneto1.0* expressing 24 hpf zebrafish embryos in response to magnetic stimulation. n=43 WT, n=25 *ß-actin::Magneto1.0* fish. Statistics determined by Chi-squared analysis, (Chi^2_3=36.51, p<0.0001). (**d**) Quantification of coiling rate in WT (uninjected) and *ß-actin::Magneto1.0* expressing zebrafish. Replicates (number of individual fish) shown in columns. Statistics determined by one-way ANOVA, Bonferroni post-test, ($F_{3,64}$=3.89, p=0.0129). ***p<0.001, *p<0.05. Data are shown as mean±SEM.

Source data

Supplementary Figure 10 Analysis of Magneto2.0 in live zebrafish.

(**a**) Maximal GCaMP3 calcium fluorescence change of mCherry+ (n=20 from 5 fish) and mCherry- (n=33 from 5 fish) neurons in response to magnetic field stimulation. Dashed line indicates average GCaMP3 fluorescence value for mCherry- neurons. (17/20 mCherry+ neurons exceed this fluorescence value). Unpaired two-

tailed t-test, (t_{51}=3.373, p=0.0014). (**b**) Schematic of behavioral paradigm for induction of zebrafish coiling behaviors using magnetic stimulation. (**c**) Schematic of Rohon-Beard neuron projections. (**d**) Magneto2.0 expression construct. Tol2: transposon site; ngn1: neurogenin-1 promoter; IRES: internal ribosomal entry site; nls: nuclear localization signal; EGFP: enhanced green fluorescent protein; polyA: polyadenylation signal. (**e-f**) *In vivo* imaging of Rohon-Beard neuron projections into the skin, n=10 fish examined per genotype. Inset: Magneto2.0+ (EGFP+/RFP+) and Magneto2.0- (EGFP–/RFP+) neurons. Data pooled from 2 injections per genotype. **p<0.01. Data shown as mean±SEM.

Source data

Supplementary Figure 11 Mouse behavioral controls.

(**a**) Quantification of the change in firing rate relative to baseline for low-frequency and high-frequency firing single units in the striatum in response to the D1R agonist SKF81297, n=7 (<5 Hz), n=8 (>5 Hz) units examined from one *Drd1a::Cre* mouse transduced with *CMV::DIO-Magneto2.0*, unpaired two-tailed t-test, (t_{13}=2.192, p=0.0472). (**b**) Picture of magnetic open field behavioral chamber. (**c**) Quantification of change in linear velocity in open field for both groups (n=6 per genotype), unpaired two-tailed t-test, (t_{10}=0.08856, p=0.9312). *p<0.05, ns: not significant. Data shown as mean±SEM.

Source data

Supplementary information

Source data

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Subjects