Dissecting neuronal circuits using chemogenetic tools

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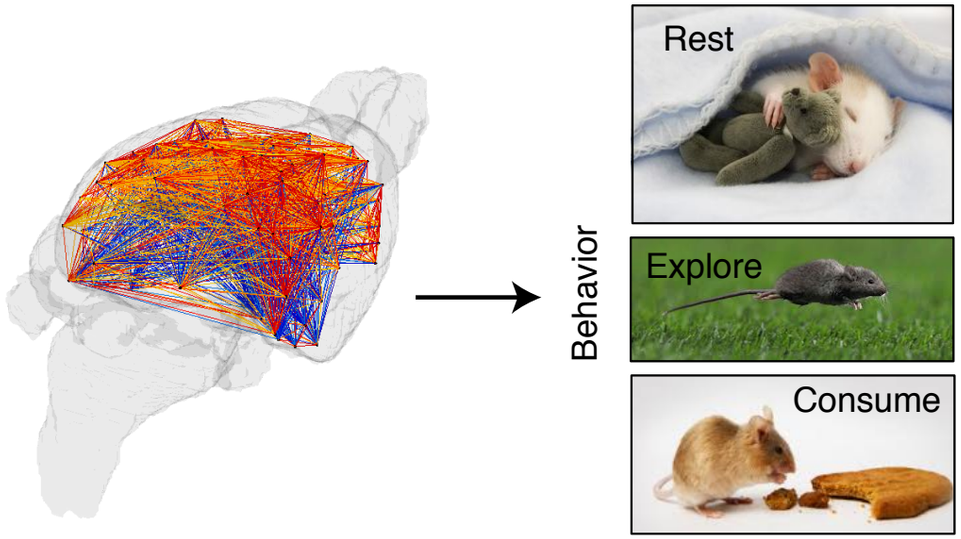
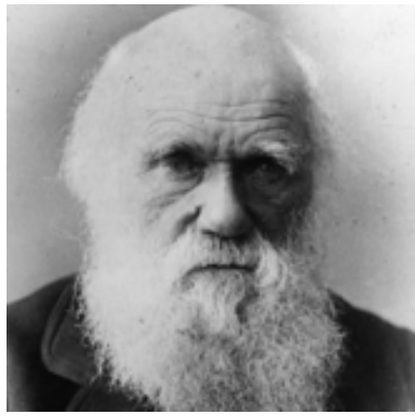
Yale School of Medicine

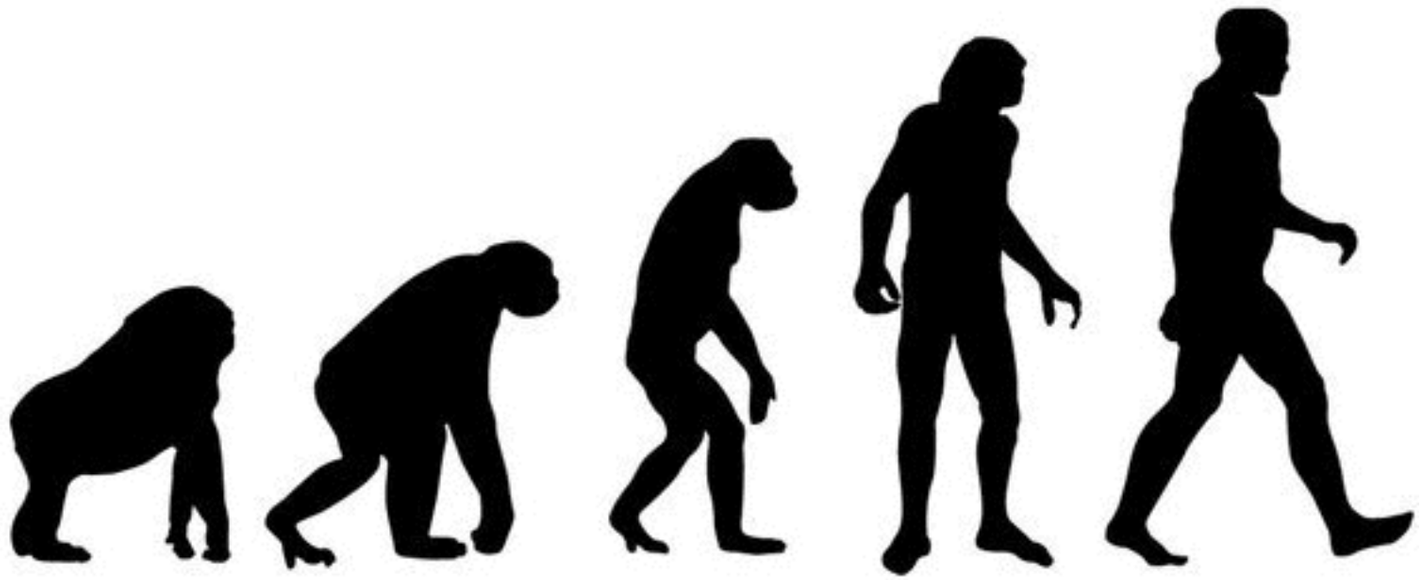
"State-of-the-art Methods in Neuroscience Research"
September 28, 2015 | Mar del Plata, Argentina

How does the brain organizes behaviors?



…evolution of human behaviors…





Darwin was the first to argue that since man had evolved from lower animals, human behaviors must have parallels in the behaviors of lower forms.

"The anti-neuronists began almost all of their studies in man where the nests reach great complexity, … making it difficult ... for their analysis. If, instead of it, **they would have started their investigations in birds or rodents**, passing afterwards to the carnivores, and undertaking finally the problem of human cerebellum, **they would have avoid many doubts, confusions and contradictions**."

Santiago Ramon y Cajal

A brief history of how we got where we are…

1839. Cell theory or ‘Cell doctrine’ | *All living things are composed of cells and cell products*.

* Schwann, Theodor (1839). Microscopic Investigations on the Accordance in the Structure and Growth of Plants and Animals. Berlin.

1873. The discovery of the ‘black reaction’ (la reazione nera) by C. Golgi | *Reticular Theory*

* Camillo Golgi

1888. First evidence the nervous system is not continuous | *Neuron Doctrine*

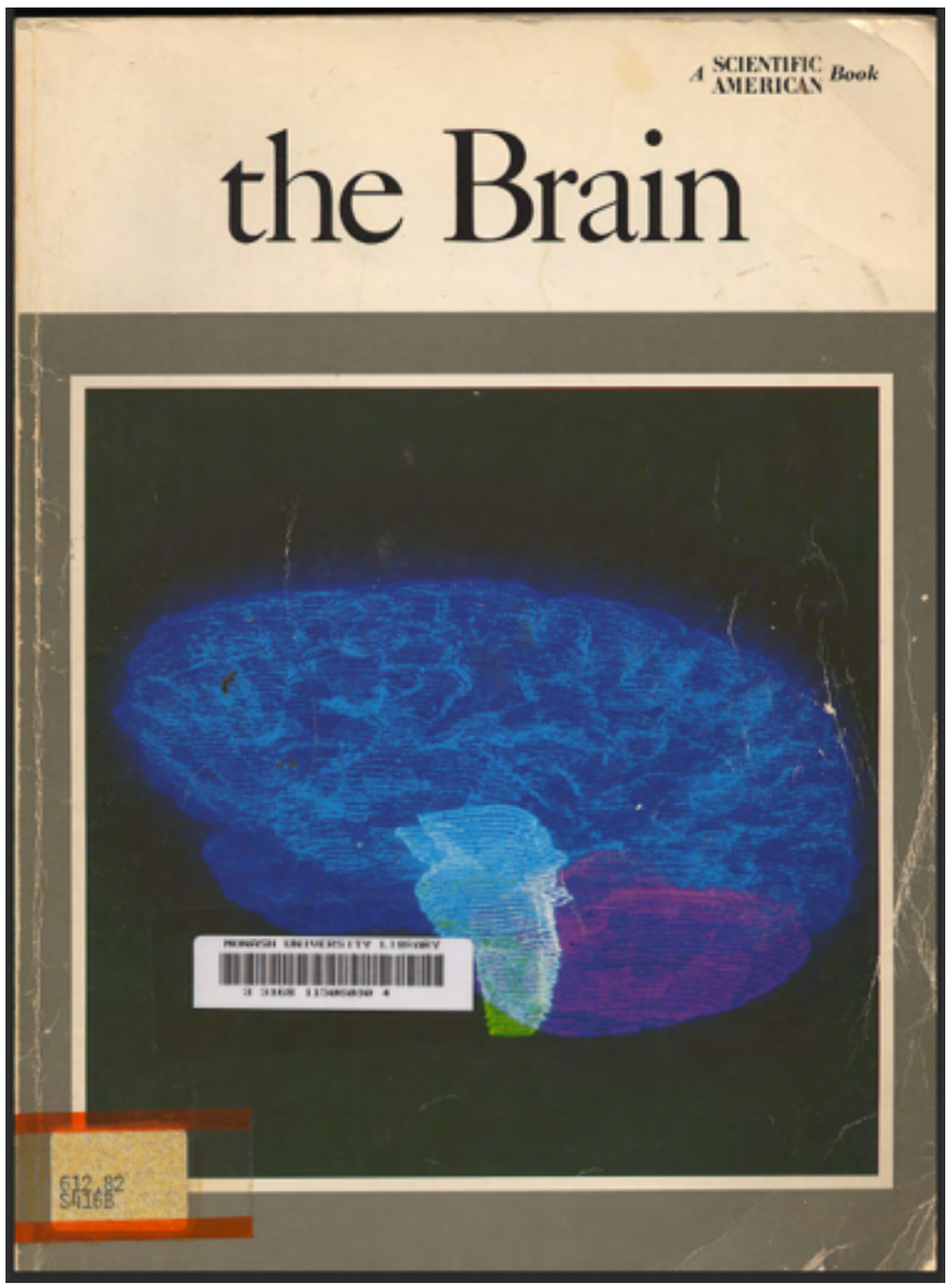
* Santiago Ramón y Cajal

1921. Nobel Prize for Sir Charles S. Sherrington for his discoveries on neural reflexes and the prediction of inhibitory and excitatory synapses.

1936. Nobel Prize for Loewi and Dale for their discoveries on chemical neurotransmission.

1950s. Anatomical structure of synapses is revealed by electron microscopy.

* George Palade, Eduardo de Robertis and George Bennett



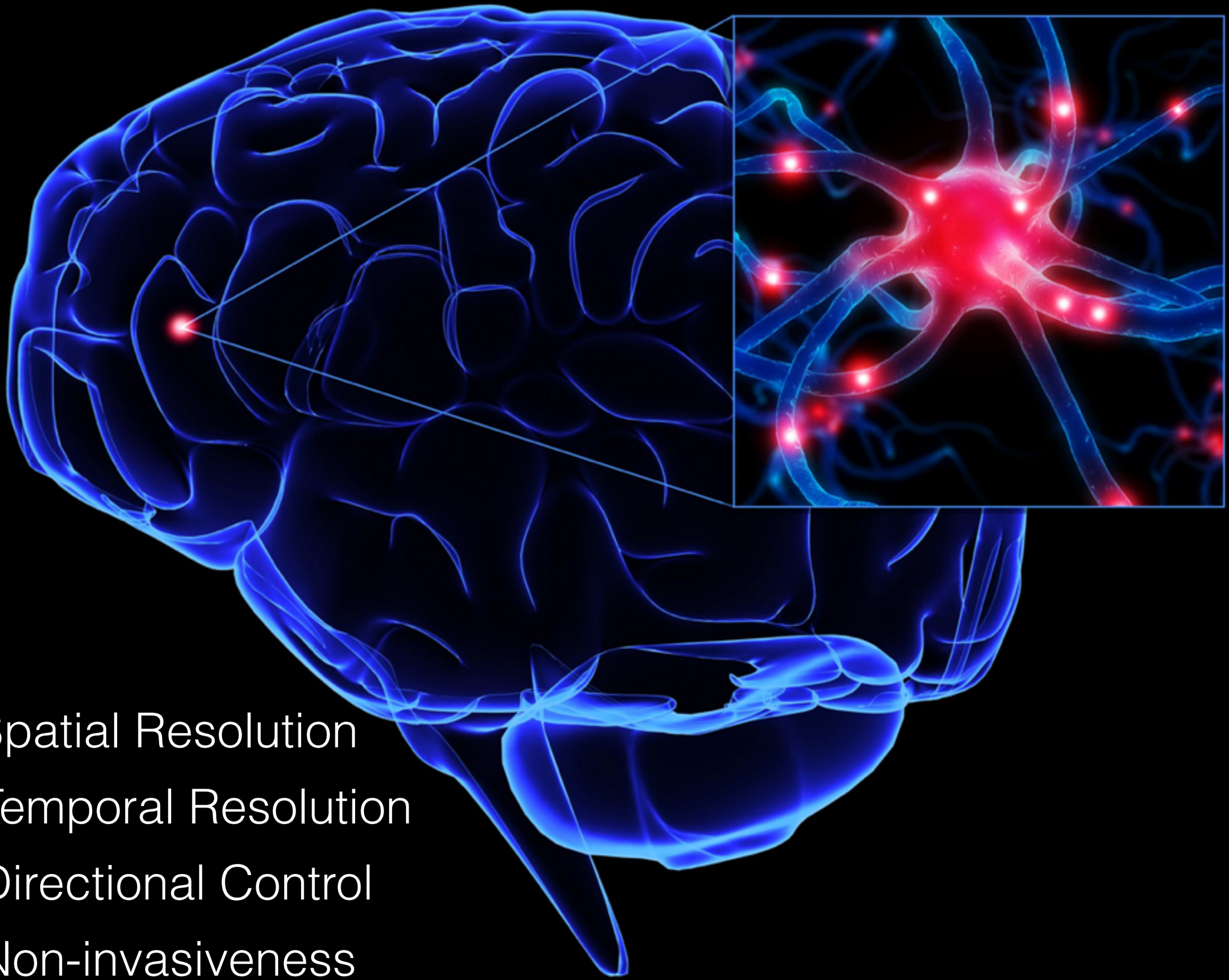
Thinking about the Brain

Reflecting on itself, the human brain has uncovered some marvelous facts. What appears to be needed for understanding how it works is new techniques for examining it and new ways of thinking about it

by F. H. C. Crick

…a method by which all neurons of just one type could be inactivated, leaving the others more or less unaltered [is needed].

A technique to control neuronal activity…



1. Spatial Resolution
2. Temporal Resolution
3. Directional Control
4. Non-invasiveness

Toolbox for neuronal control

Lesion	Mechanic or electrolytic
Electric stimulation	Recording electrodes
Optogenetics	Light (via optic fibers)
★ Chemogenetics	Chemicals
Magnetogenetics	Magnetic field
Sonogenetics	Ultrasound

Chemogenetic tools

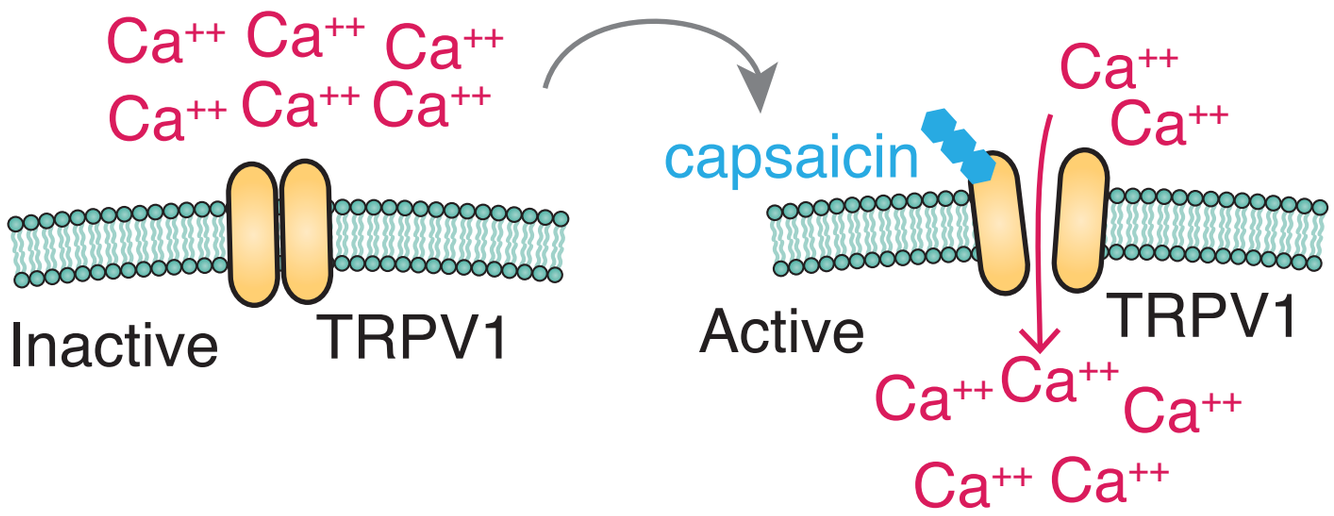
A tool to alter neuron signaling using small-molecule-mediated activation of engineered proteins.

Based on ion channel receptors

Based on G Protein-coupled receptors

Others

Chemogenetic control via TRPV1 channels

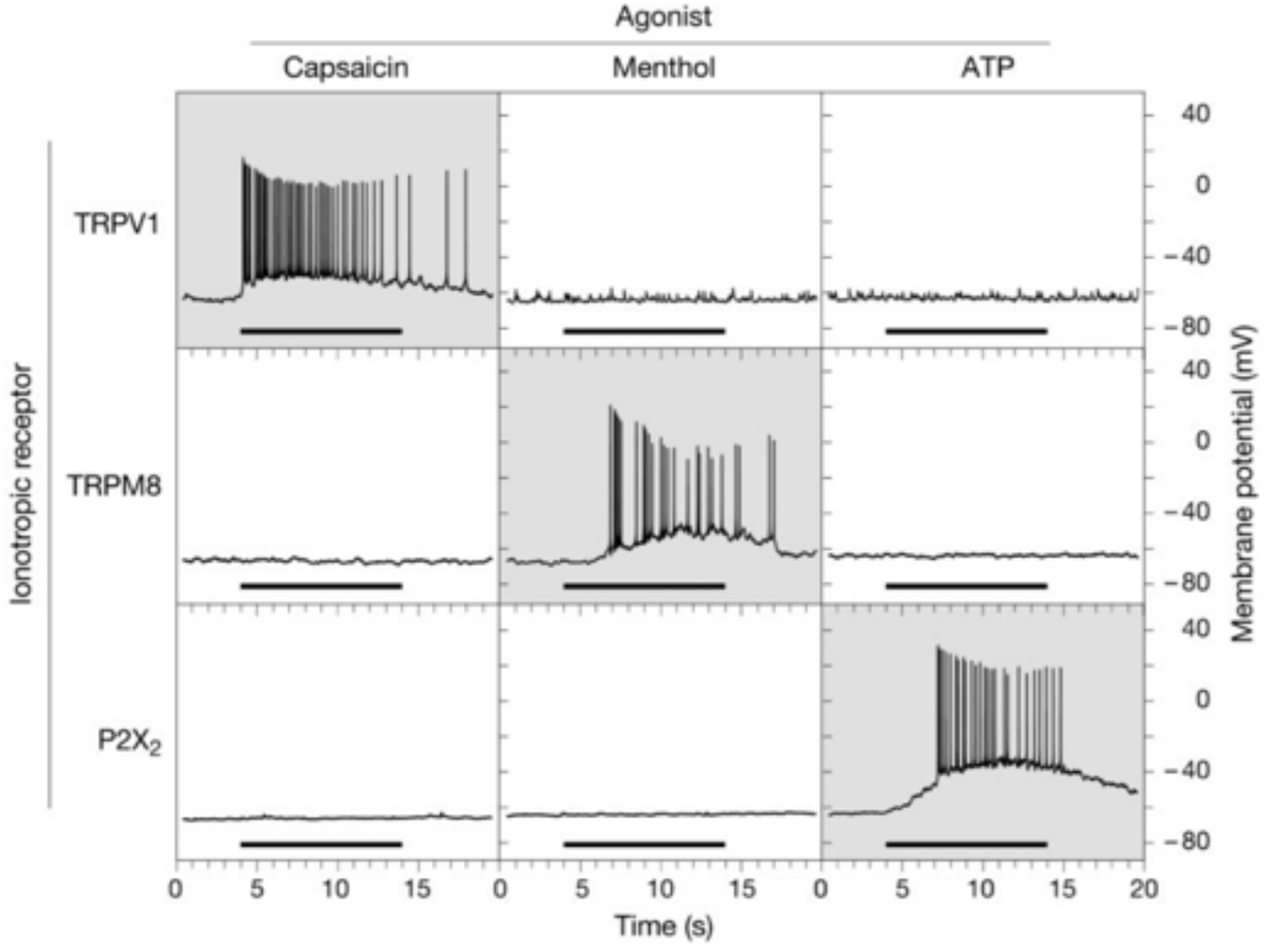


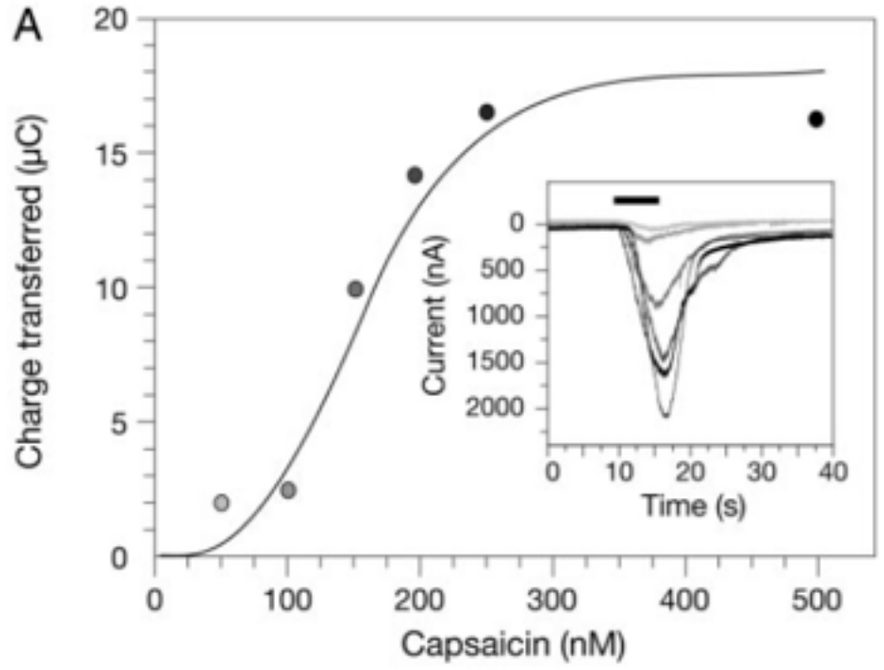
Chemogenetic control via TRPV1 channels

1352–1357 | PNAS | February 4, 2003 | vol. 100 | no. 3 www.pnas.org/cgi/doi/10.1073/pnas.242738899

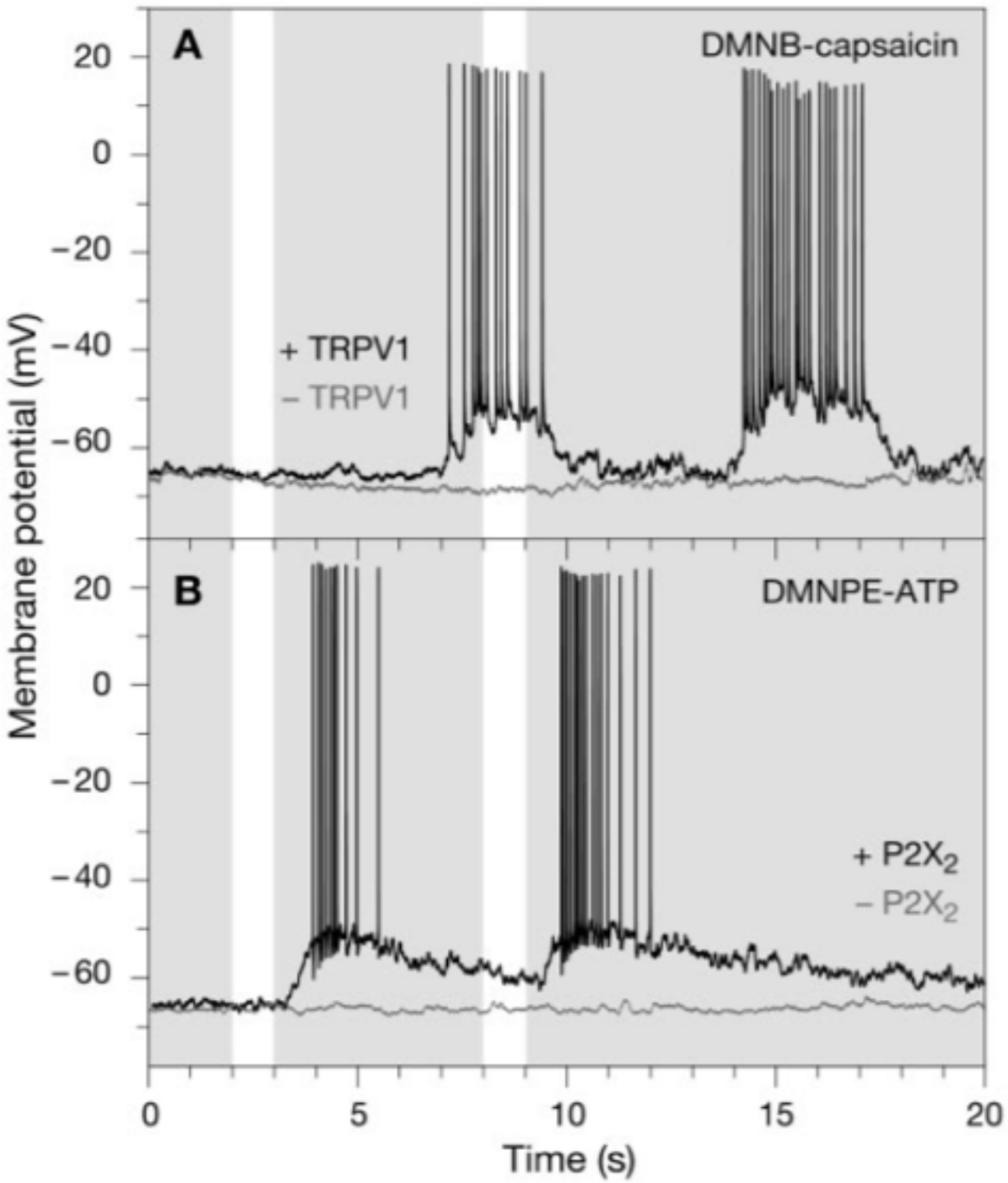
Photochemical gating of heterologous ion channels: Remote control over genetically designated populations of neurons

Boris V. Zemelman*, Nasri Nesnas†, Georgia A. Lee*, and Gero Miesenböck*‡





Chemogenetic control via TRPV1 channels



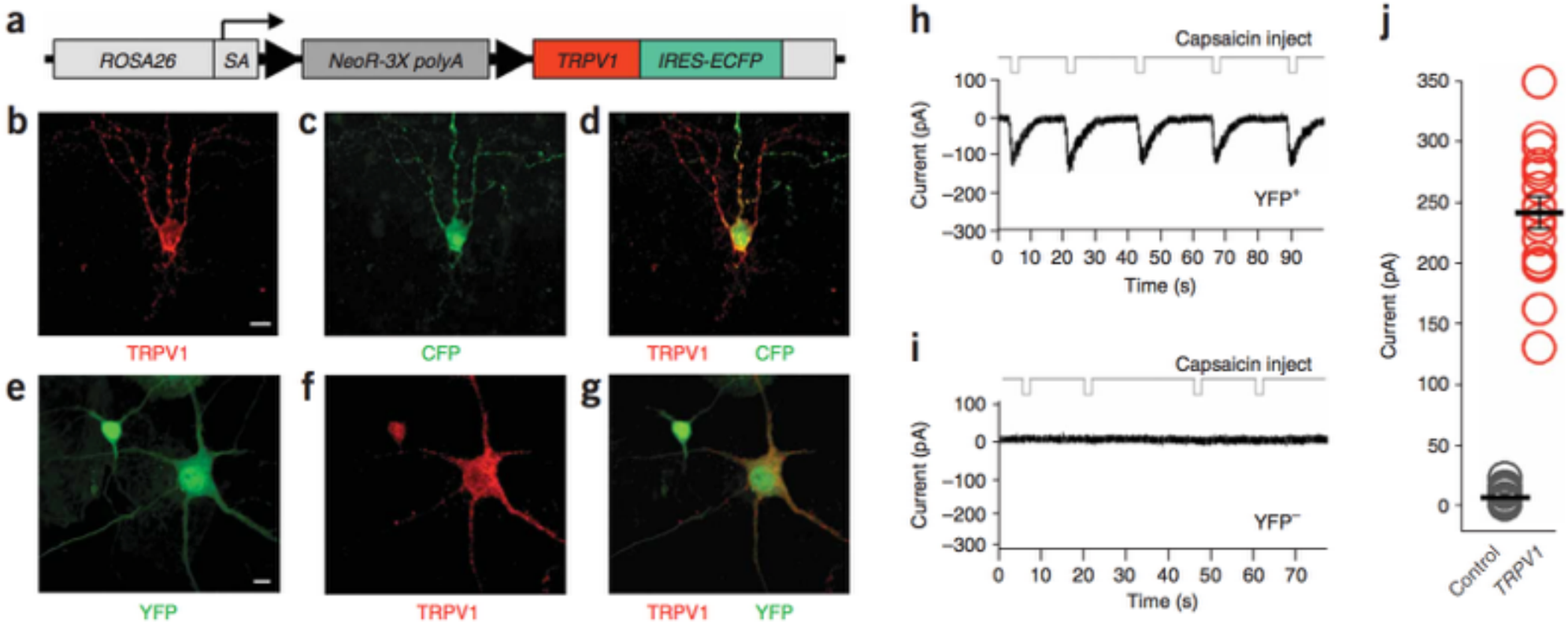
First experimental evidence of ON and OFF kinetics of neuronal activity using genetically encoded tools

Chemogenetic control via TRPV1 channels

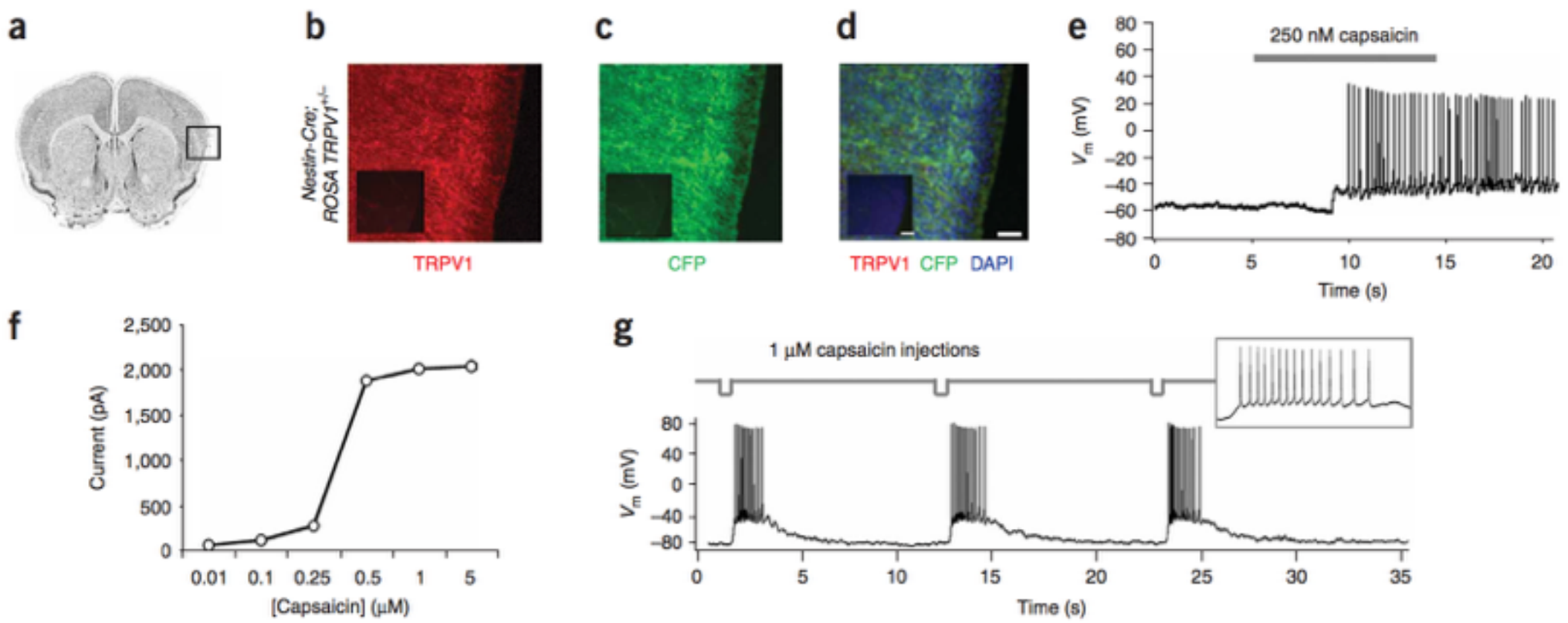
NATURE METHODS | VOL.5 NO.4 | APRIL 2008 | 299

Genetic control of neuronal activity in mice conditionally expressing *TRPV1*

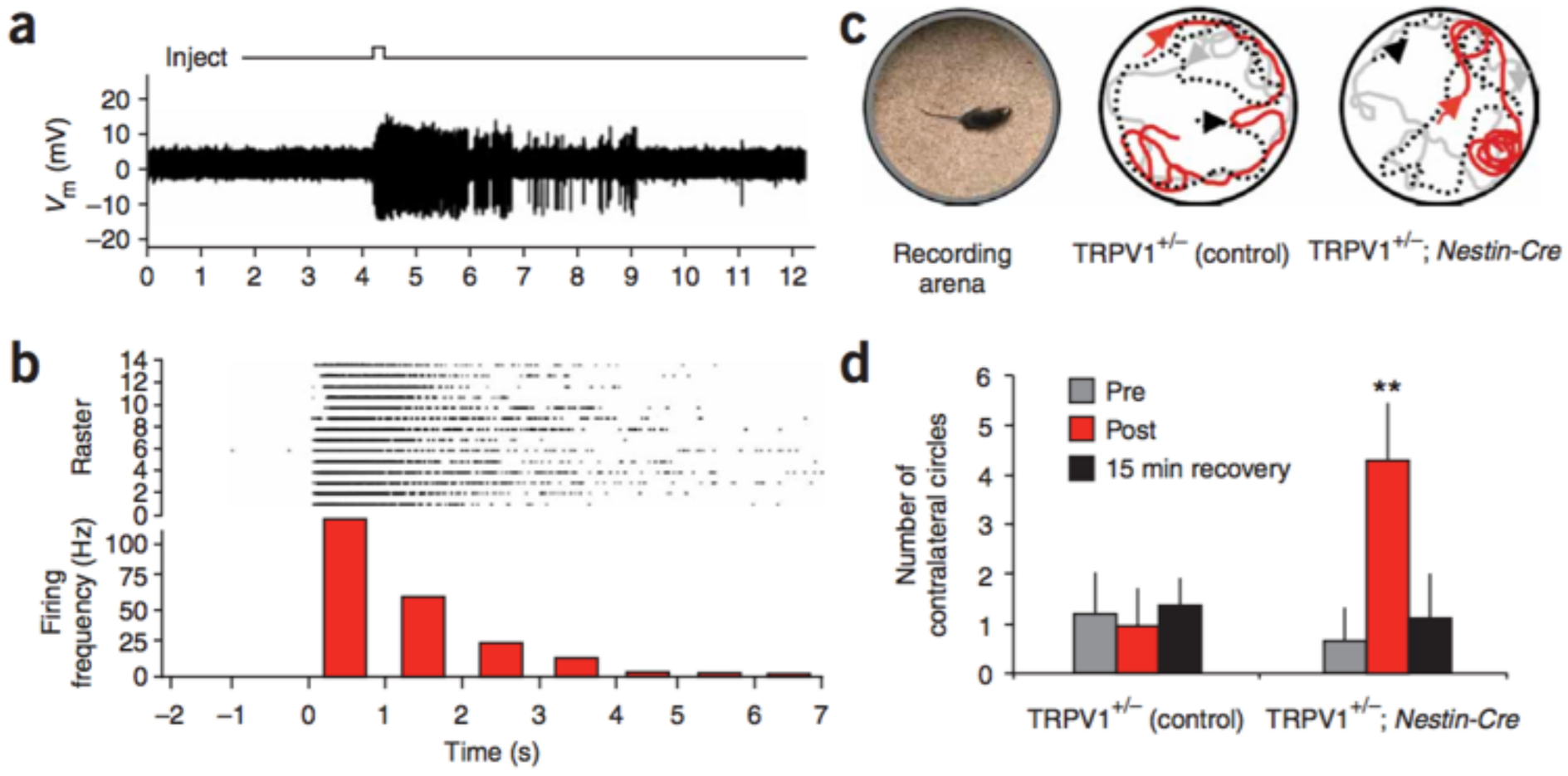
Benjamin R Arenkiel, Marguerita E Klein,
Ian G Davison, Lawrence C Katz & Michael D Ehlers



Chemogenetic control via TRPV1 channels



Chemogenetic control via TRPV1 channels



Chemogenetic control via TRPV1 channels

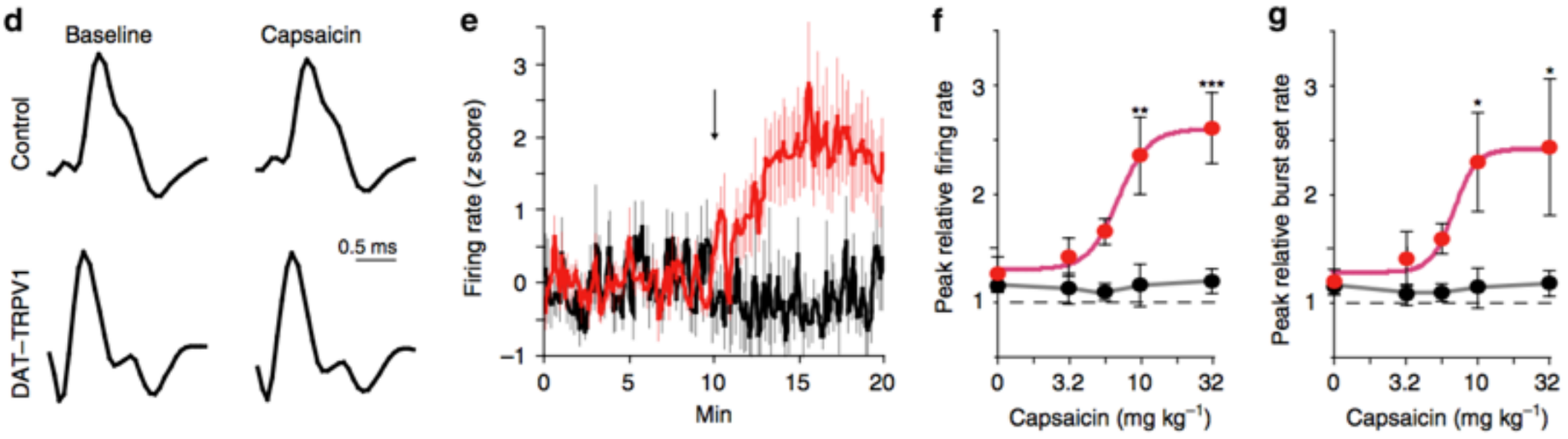
ARTICLE

Received 13 Oct 2011 | Accepted 13 Feb 2012 | Published 20 Mar 2012

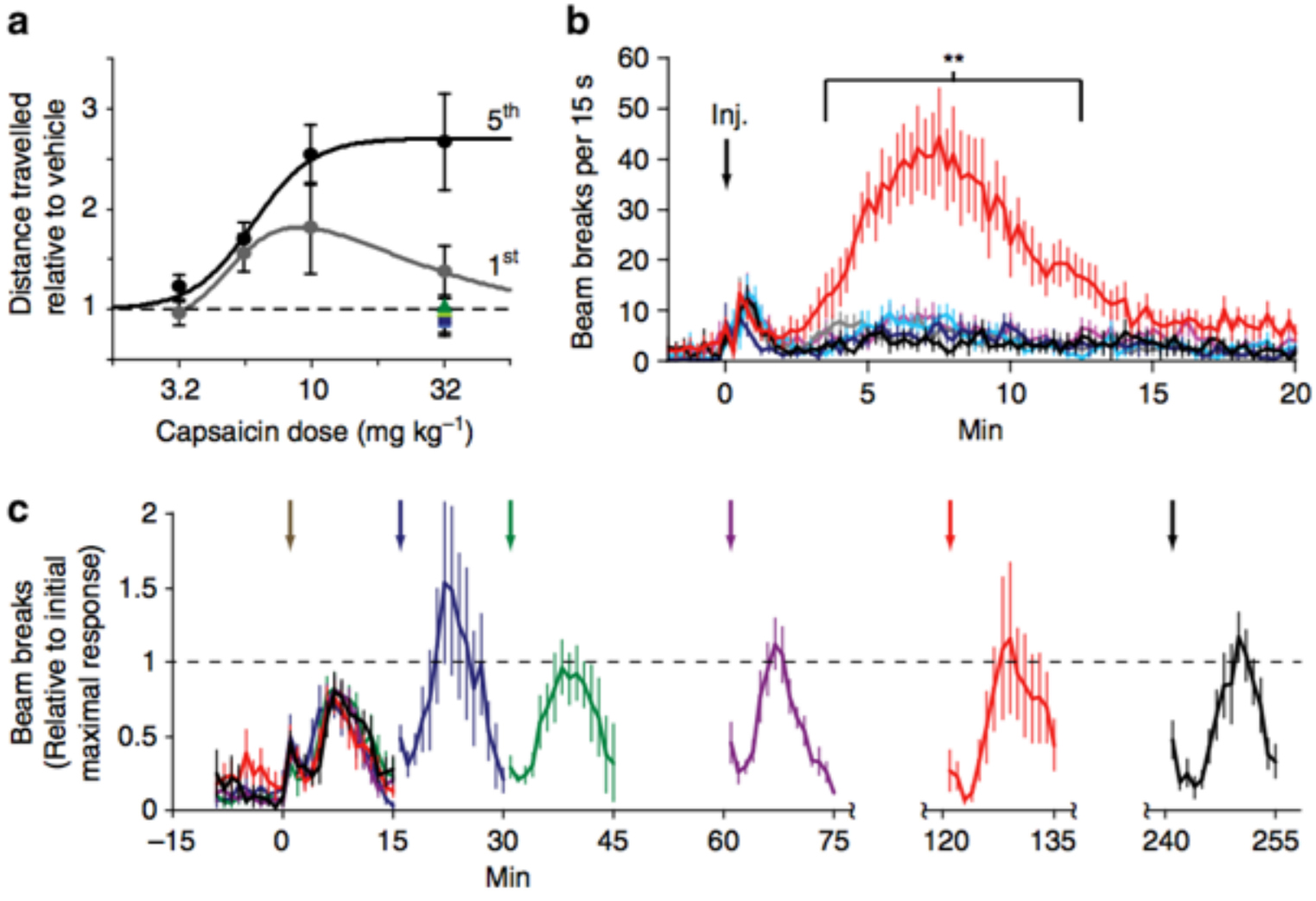
DOI: 10.1038/ncomms1749

Transient activation of specific neurons in mice by selective expression of the capsaicin receptor

Ali D. Güler[1], Aundrea Rainwater[1], Jones G. Parker[1], Graham L. Jones[2], Emanuela Argilli[3], Benjamin R. Arenkiel[4], Michael D. Ehlers[5], Antonello Bonci[3,6,7], Larry S. Zweifel[2] & Richard D. Palmiter[1]



Chemogenetic control via TRPV1 channels



Chemogenetic control via TRPV1 channels

Cell *159*, 306–317, October 9, 2014

O-GlcNAc Transferase Enables AgRP Neurons to Suppress Browning of White Fat

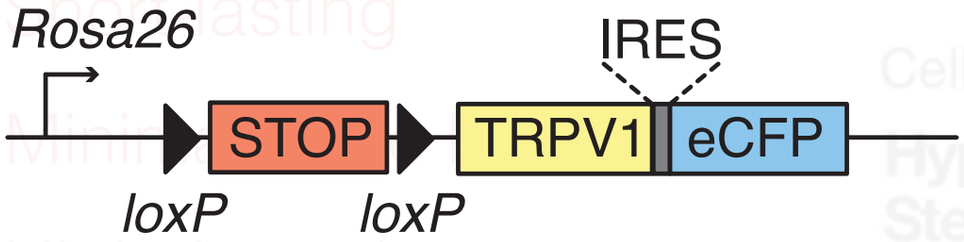
Hai-Bin Ruan,[1,2] Marcelo O. Dietrich,[1,2,5,6] Zhong-Wu Liu,[1,2] Marcelo R. Zimmer,[1,2,6] Min-Dian Li,[1,2,3] Jay Prakash Singh,[1,2] Kaisi Zhang,[1,2,3] Ruonan Yin,[1,2] Jing Wu,[1,2] Tamas L. Horvath,[1,2,4,5,*] and Xiaoyong Yang[1,2,3,*]

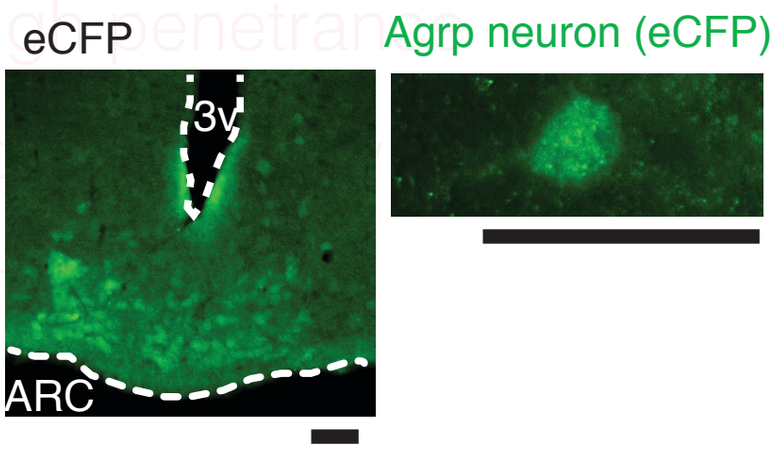
Cell *160*, 1–11, March 12, 2015

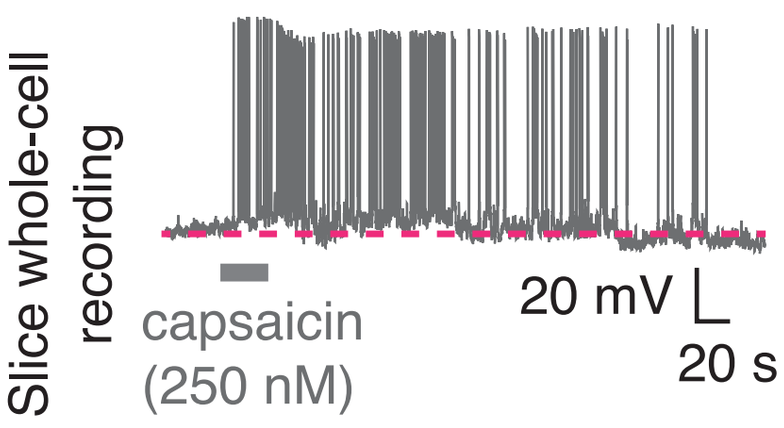
Hypothalamic Agrp Neurons Drive Stereotypic Behaviors beyond Feeding

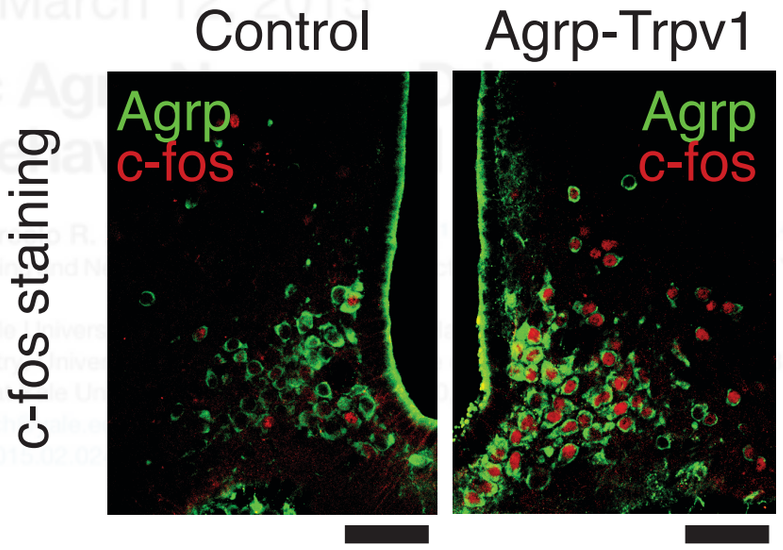
Marcelo O. Dietrich,[1,2,3,*] Marcelo R. Zimmer,[1,3] Jeremy Bober,[1] and Tamas L. Horvath[1,2,4]
[1]Program in Integrative Cell Signaling and Neurobiology of Metabolism, Section of Comparative Medicine, Yale University School of Medicine, New Haven, CT 06520, USA
[2]Department of Neurobiology, Yale University School of Medicine, New Haven, CT 06520, USA
[3]Graduate Program in Biochemistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS 90035, Brazil
[4]Kavli Institute for Neuroscience at Yale University, New Haven, CT 06520, USA
*Correspondence: marcelo.dietrich@yale.edu
http://dx.doi.org/10.1016/j.cell.2015.02.024

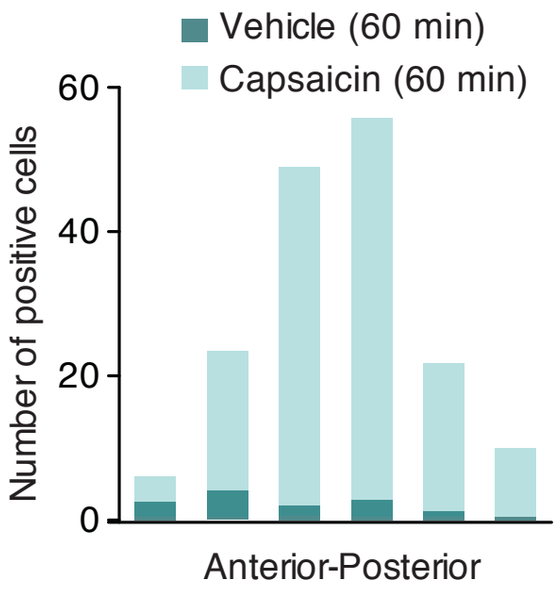
Chemogenetic control via TRPV1 channels





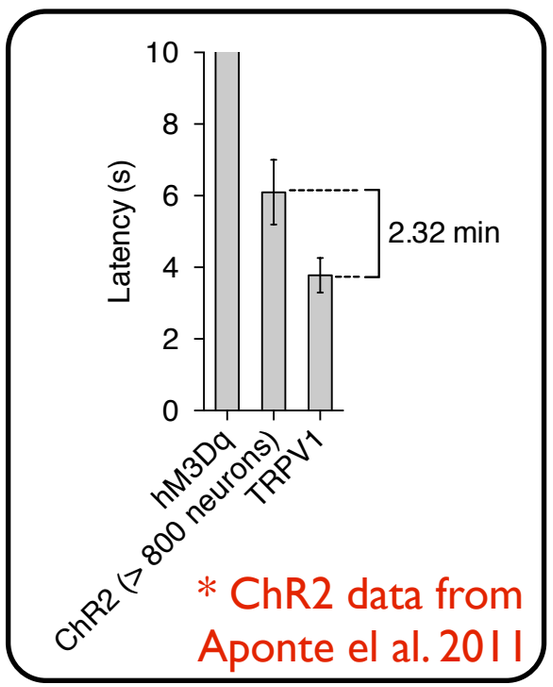






* Cell 2014; Cell 2015.

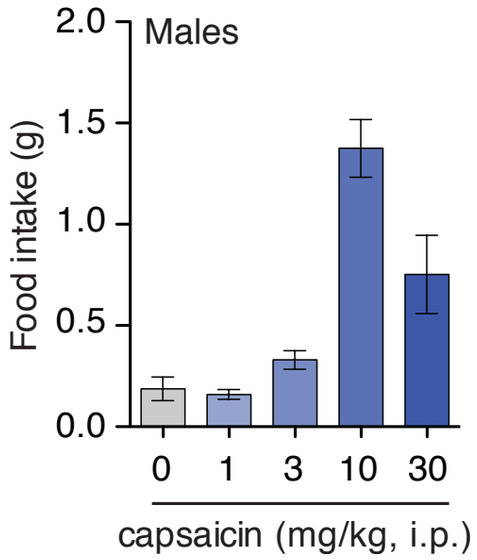
Agrp-Trpv1 mouse
injected with vehicle

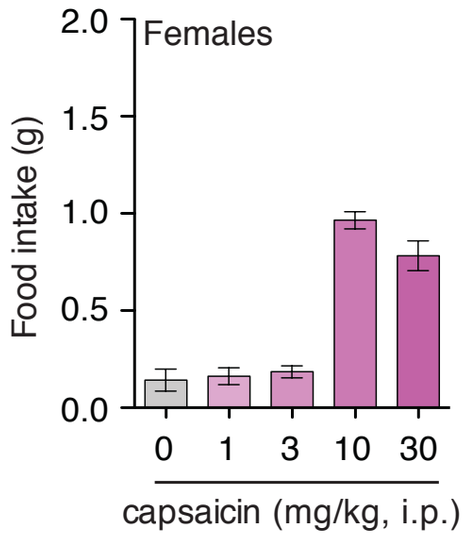


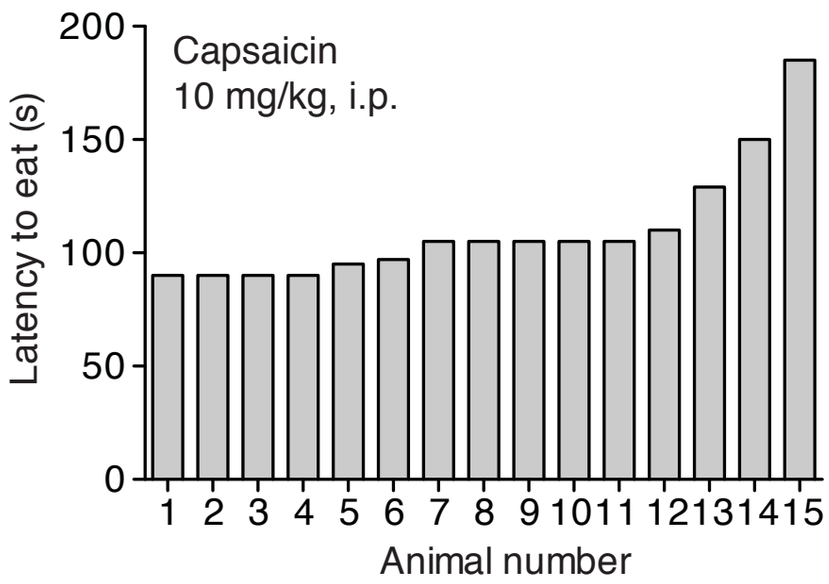
Latency to start eating = 1m55s

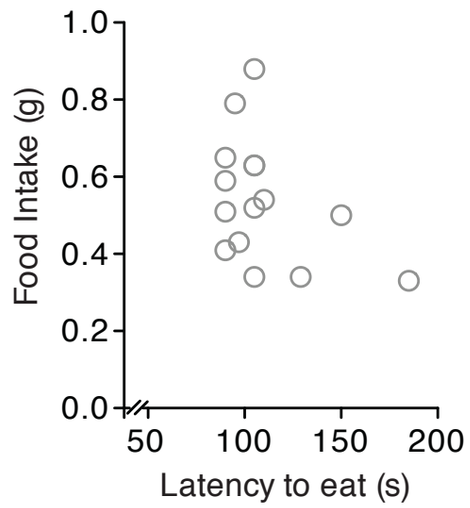
Agrp-Trpv1 mouse
injected with capsaicin

Chemogenetic control via TRPV1 channels

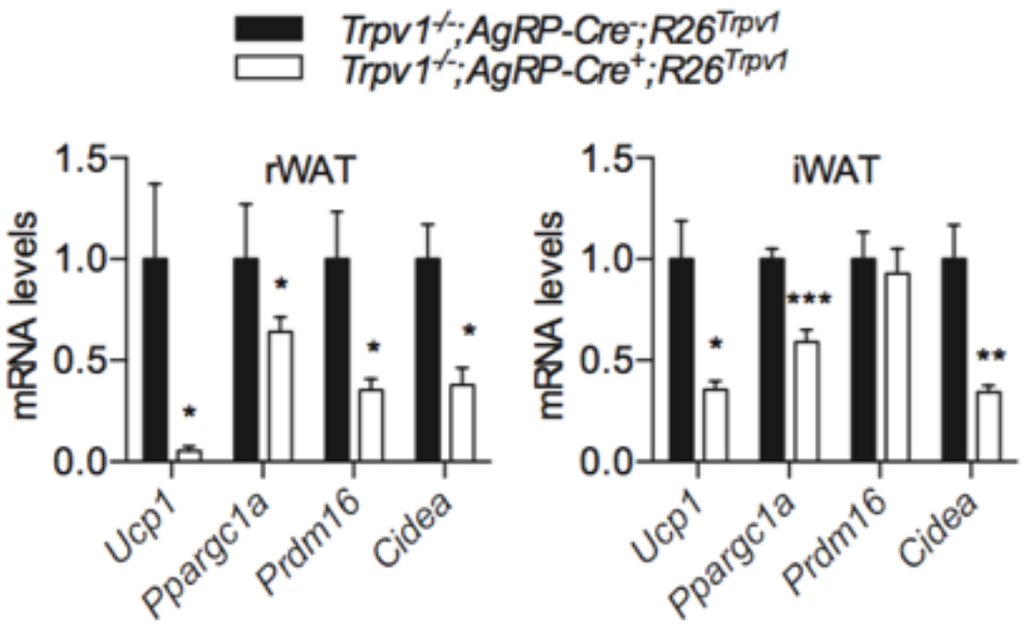




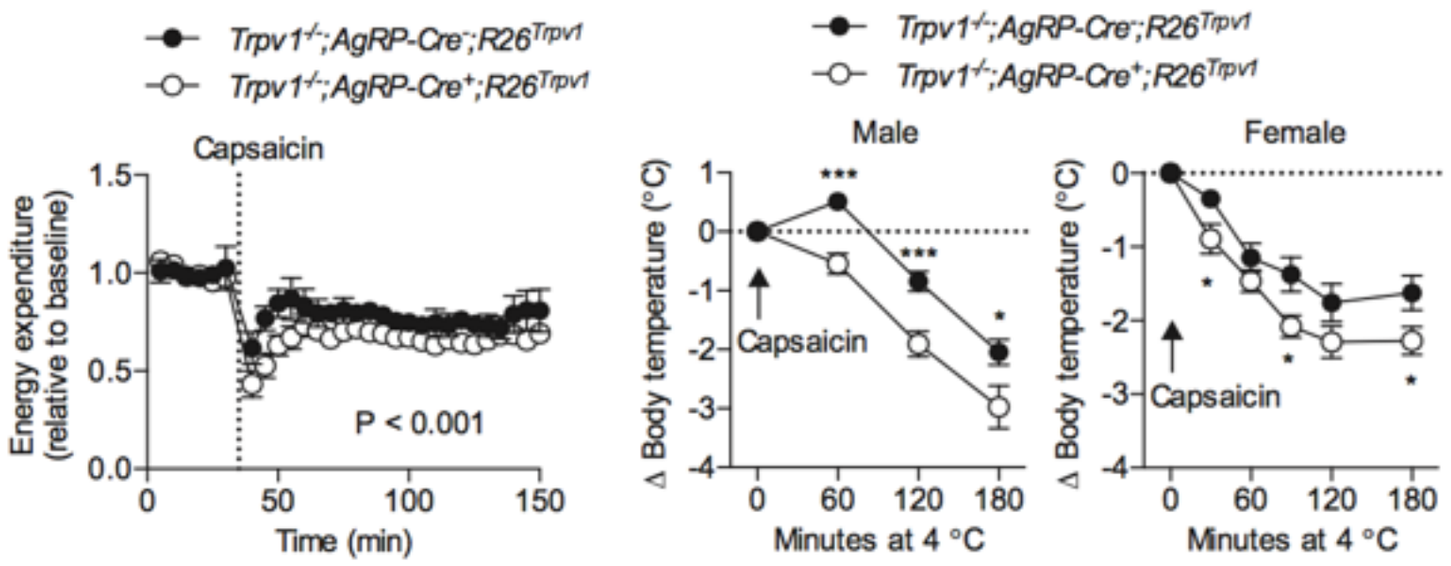




Chemogenetic control via TRPV1 channels



Using these tools to study neuronal control of physiology.



Chemogenetic control via TRPV1 channels

Positive or neutral:

Good temporal resolution

Minimal or no brain lesion

High throughput

Low variability

Reversible

Allows developmental studies

Negative:

Need to use Trpv1 KO background to avoid side effects of the agonist

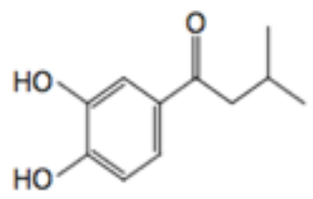
High doses of capsaicin can kill neurons

No directional control - mutant Trpv1 channels might have inhibitory properties

Q & A

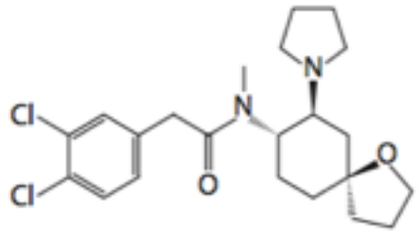
Chemogenetic control via G protein-coupled receptors

Allele-specific genetically encoded receptor



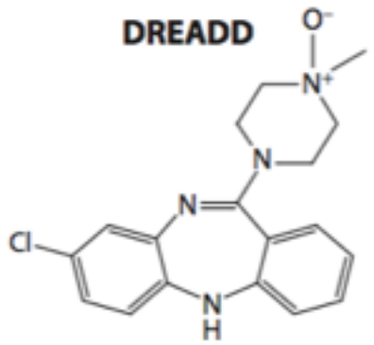
1-(3′,4′-dihydroxyphenyl)-3-methyl-L-butanone

RASSL



Spiradoline

DREADD



Clozapine N-oxide

1991 1998 2007

Annu. Rev. Neurosci. 2014. 37:387–407

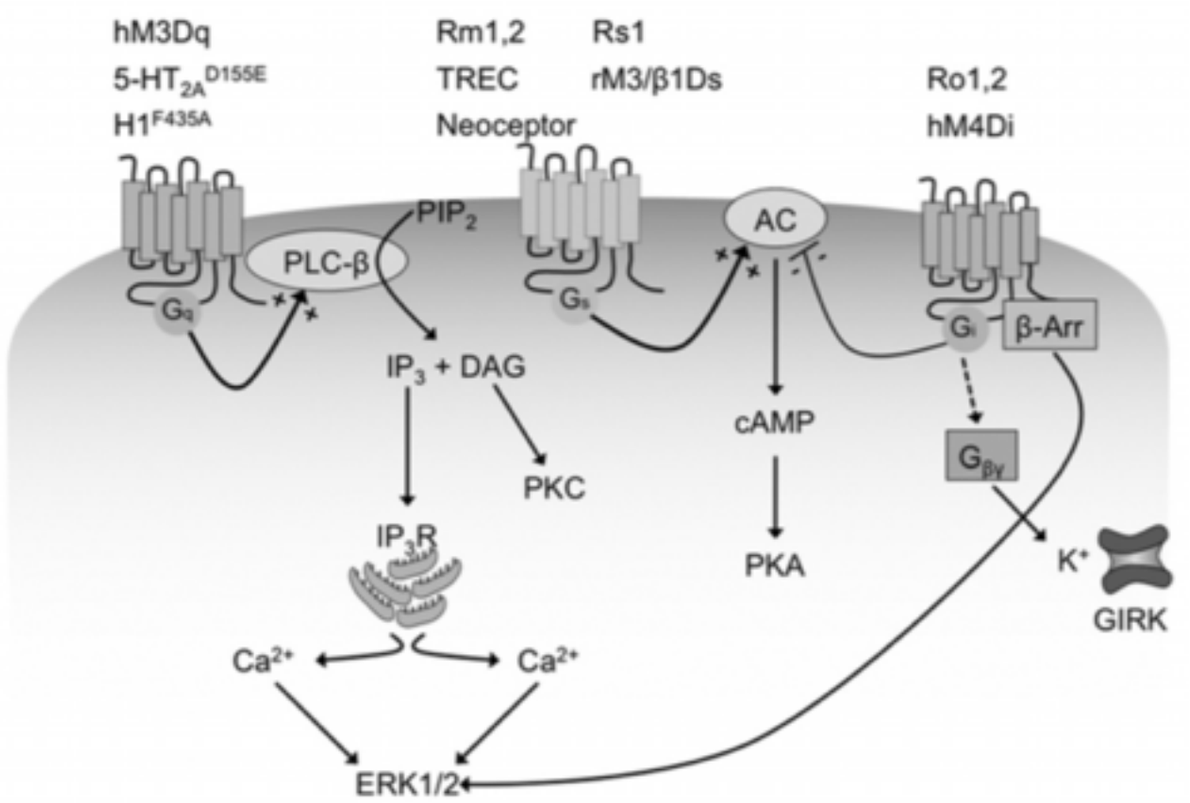
Chemogenetic Tools to Interrogate Brain Functions

Scott M. Sternson[1] and Bryan L. Roth[2]

[1]Janelia Farm Research Campus, Howard Hughes Medical Institute, Ashburn, Virginia 20147; email: sternsons@janelia.hhmi.org

[2]Department of Pharmacology and Division of Chemical Biology and Medicinal Chemistry, University of North Carolina Chapel Hill School of Medicine, Chapel Hill, North Carolina 27599; email: bryan_roth@med.unc.edu

Chemogenetic control via G protein-coupled receptors



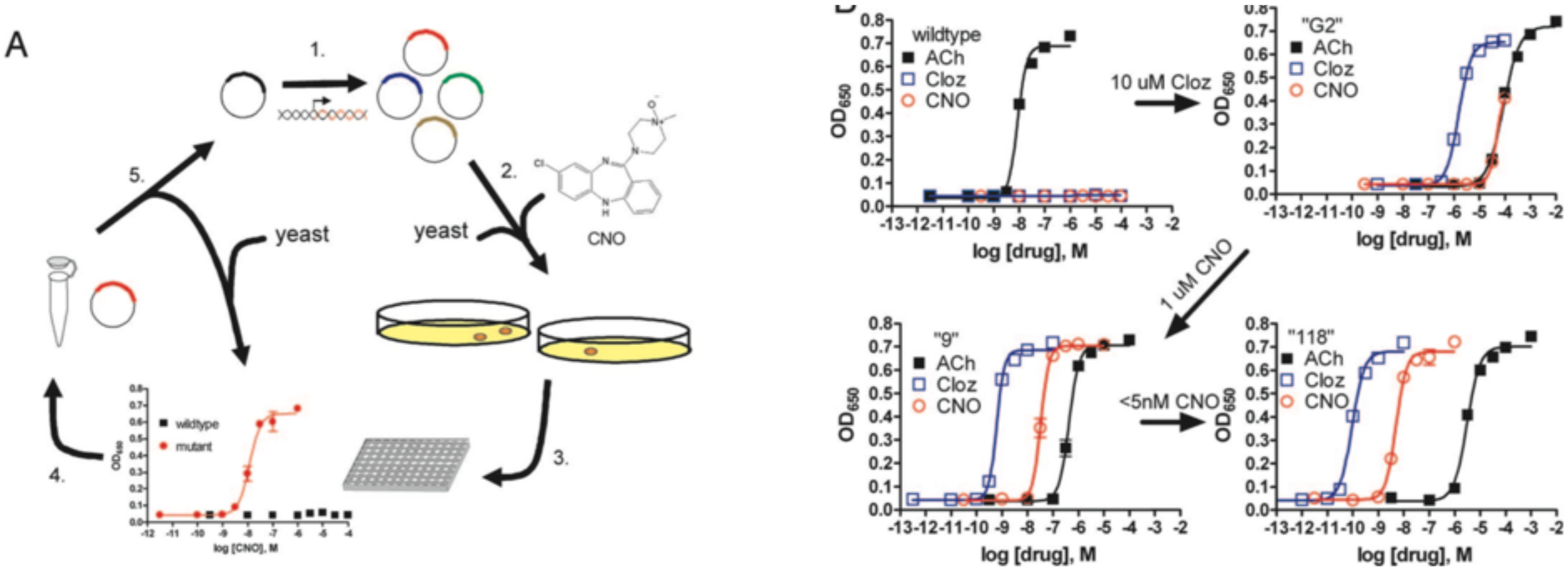
Chemogenetic control via G protein-coupled receptors

PNAS | March 20, 2007 | vol. 104 | no. 12 | 5163–5168

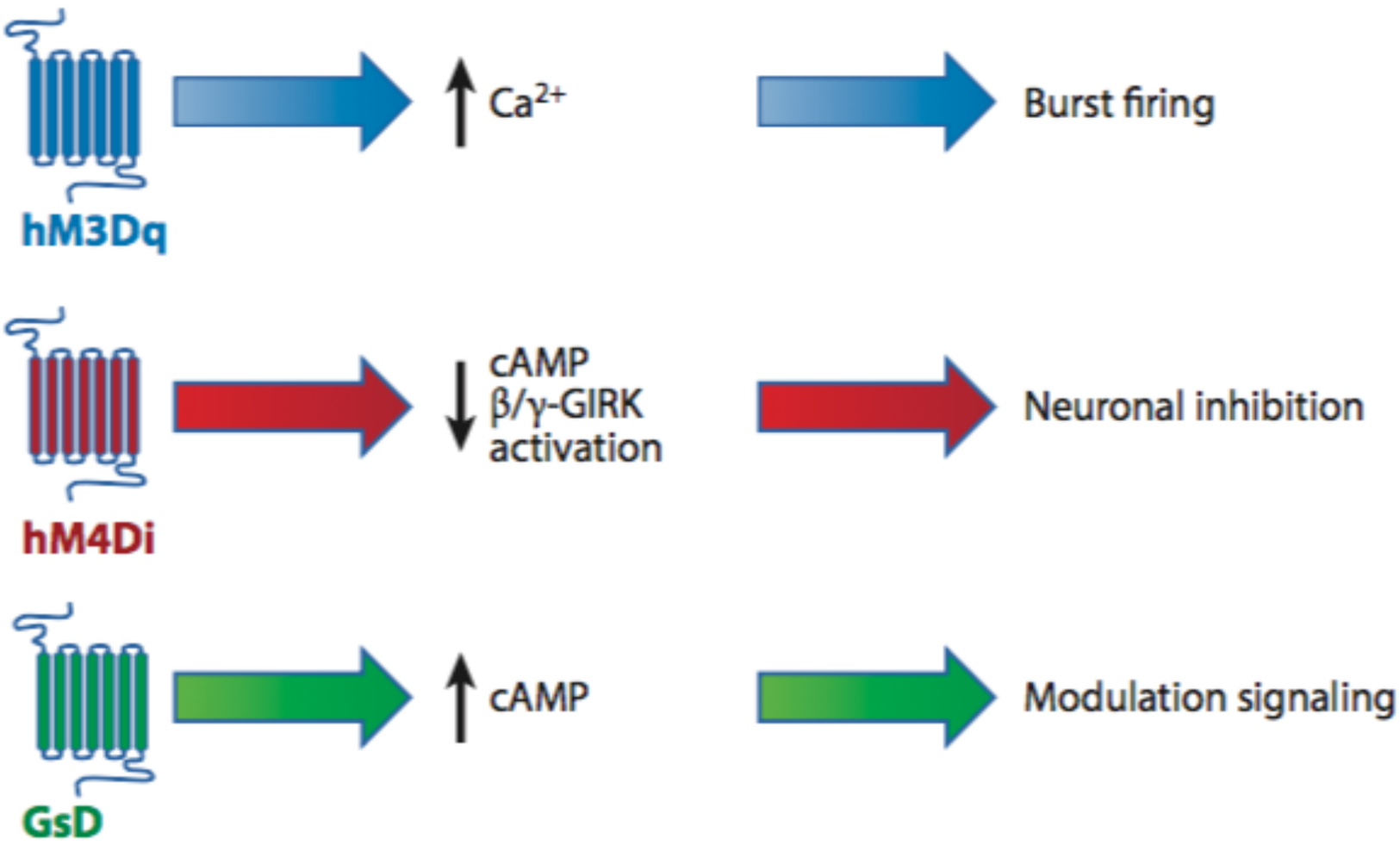
Evolving the lock to fit the key to create a family of G protein-coupled receptors potently activated by an inert ligand

Blaine N. Armbruster*, Xiang Li†, Mark H. Pausch‡, Stefan Herlitze†, and Bryan L. Roth*†§¶

Departments of *Biochemistry, †Neurosciences, and §Psychiatry, Case Western Reserve University School of Medicine, Cleveland, OH 44106; ‡Discovery Neuroscience, Wyeth Research, Princeton, NJ 08543-8000; and ¶Department of Pharmacology, University of North Carolina Medical School, Chapel Hill, NC 27705



Chemogenetic control via G protein-coupled receptors



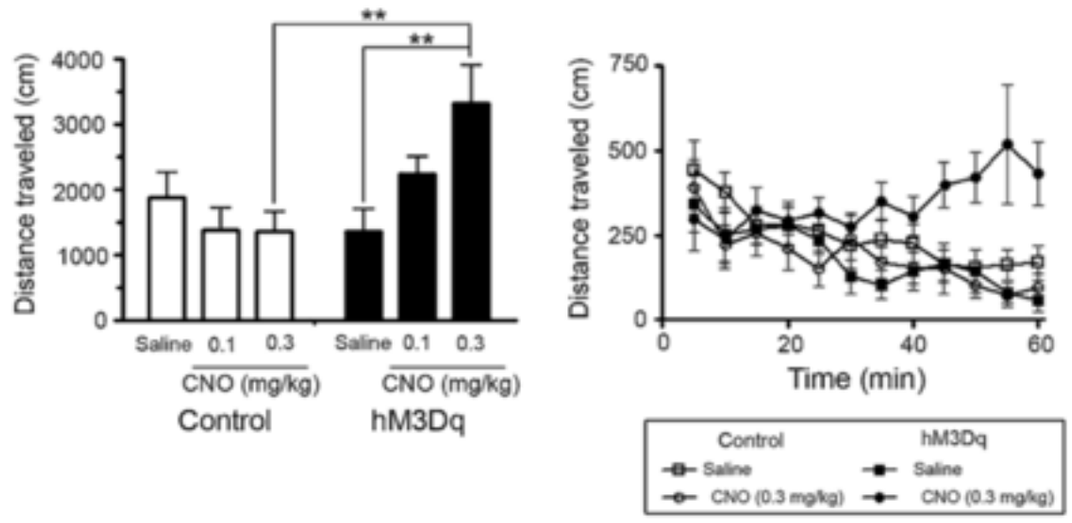
Chemogenetic control via G protein-coupled receptors

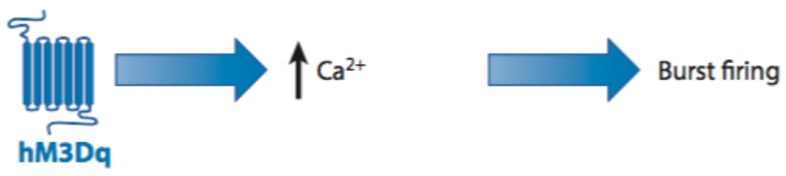
Neuron *63*, 27–39, July 16, 2009 ©2009 Elsevier Inc. **27**

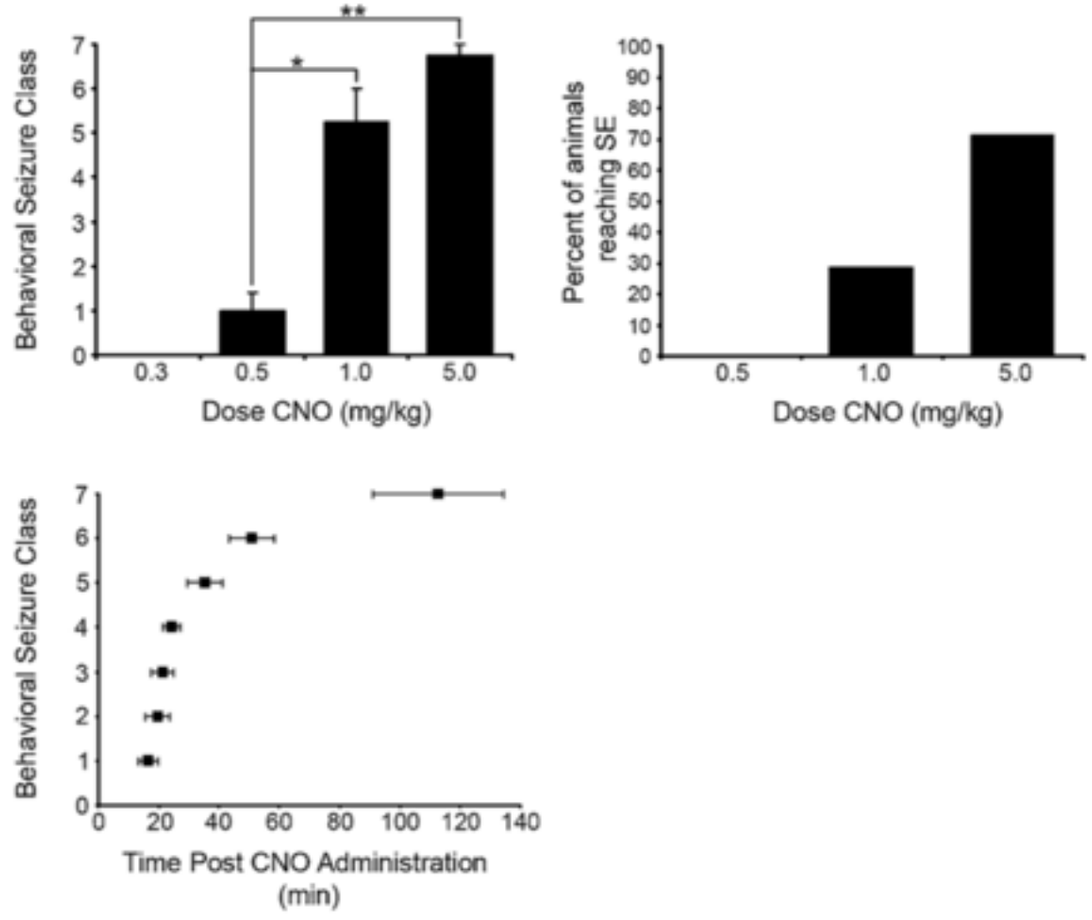
Neuron
Neurotechnique

Remote Control of Neuronal Activity in Transgenic Mice Expressing Evolved G Protein-Coupled Receptors

Georgia M. Alexander,[10,12] Sarah C. Rogan,[2,12] Atheir I. Abbas,[11] Blaine N. Armbruster,[2] Ying Pei,[2] John A. Allen,[2,7] Randal J. Nonneman,[7] John Hartmann,[1] Sheryl S. Moy,[3,7] Miguel A. Nicolelis,[10] James O. McNamara,[10,*] and Bryan L. Roth[2,3,4,5,6,7,8,9,*]





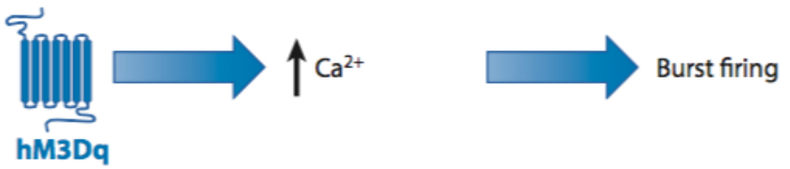


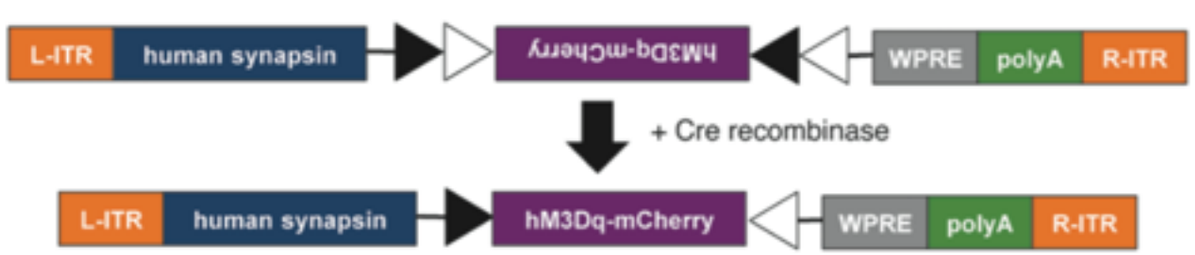
Chemogenetic control via G protein-coupled receptors

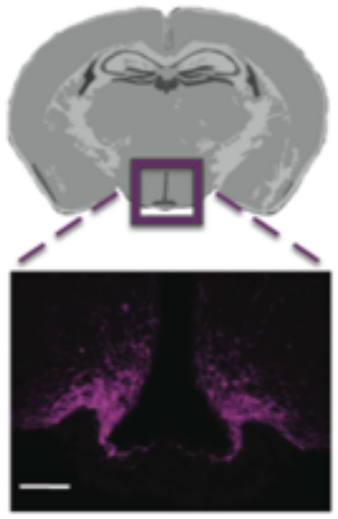
The Journal of Clinical Investigation http://www.jci.org Volume 121 Number 4 April 2011

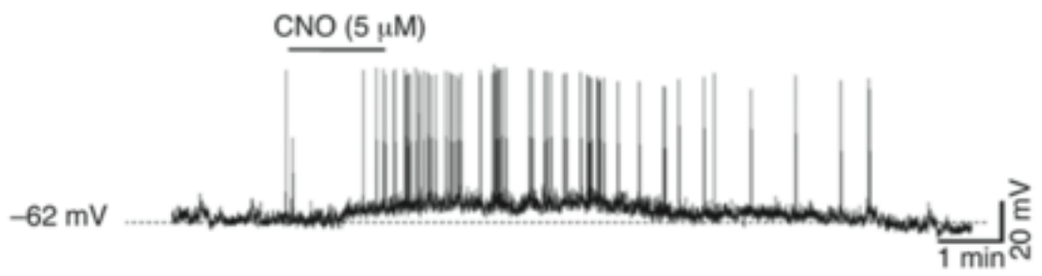
Rapid, reversible activation of AgRP neurons drives feeding behavior in mice

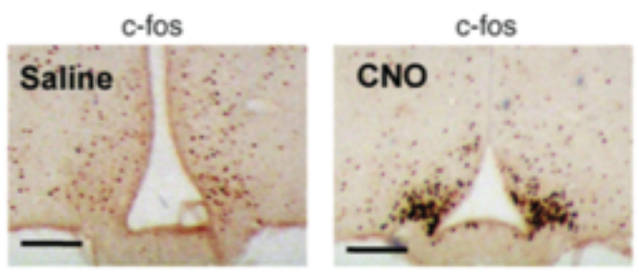
Michael J. Krashes,[1] Shuichi Koda,[1,2] ChianPing Ye,[1] Sarah C. Rogan,[3] Andrew C. Adams,[1] Daniel S. Cusher,[1] Eleftheria Maratos-Flier,[1] Bryan L. Roth,[3] and Bradford B. Lowell[1]



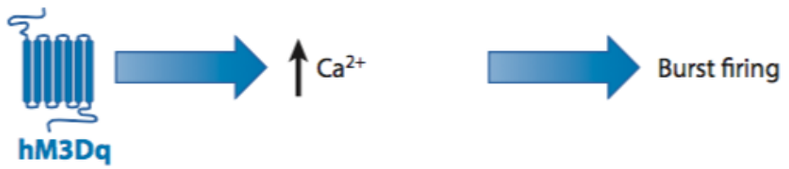


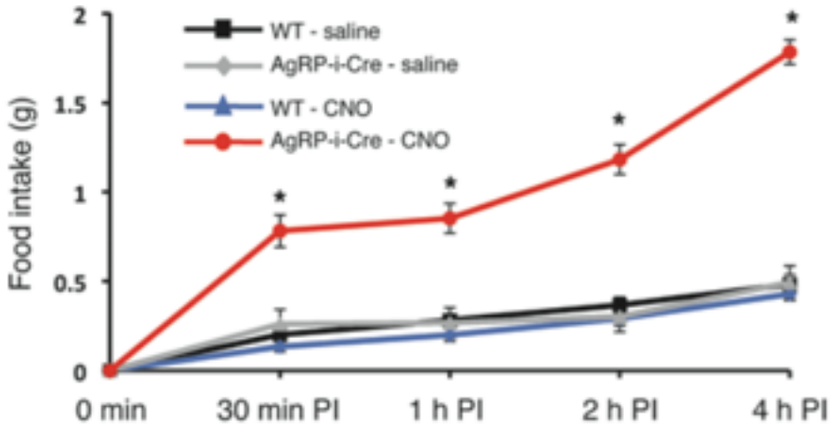


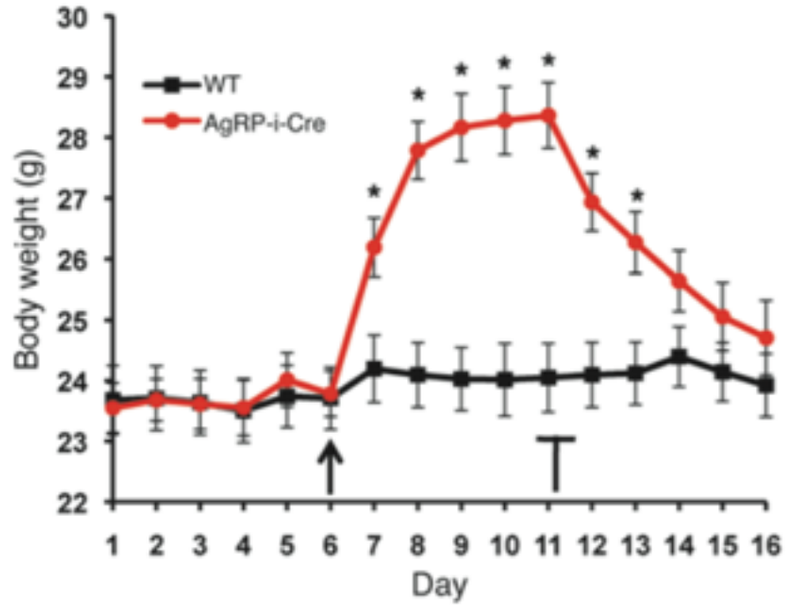


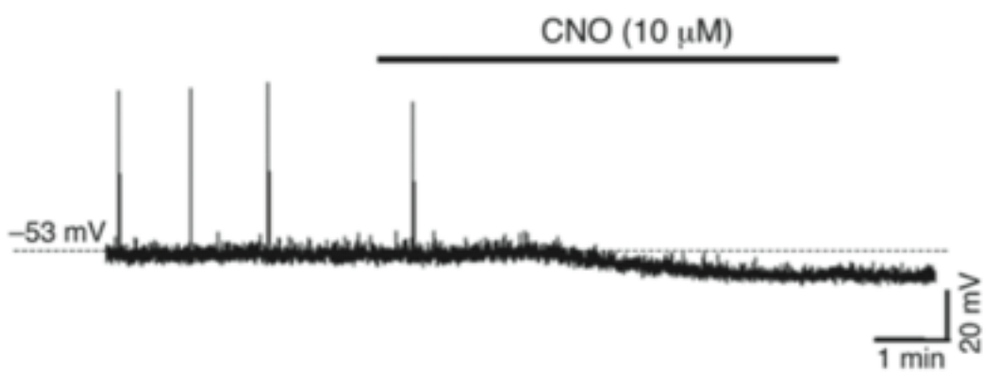


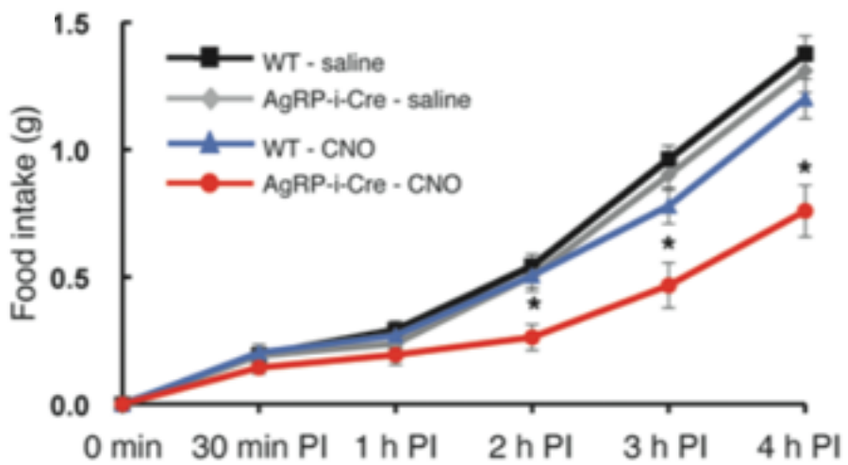
Chemogenetic control via G protein-coupled receptors









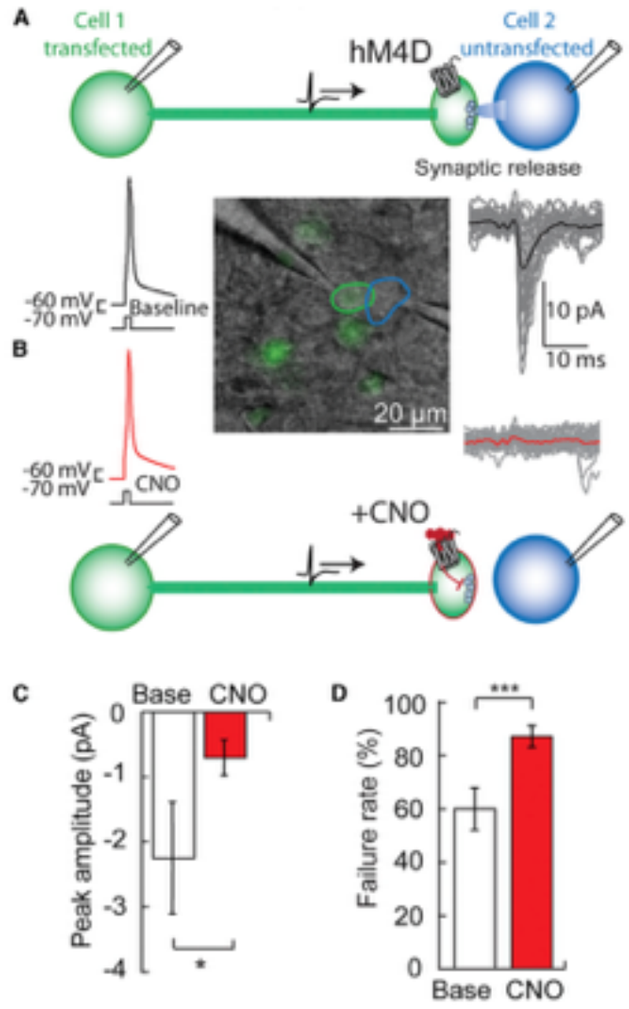


Chemogenetic control via G protein-coupled receptors

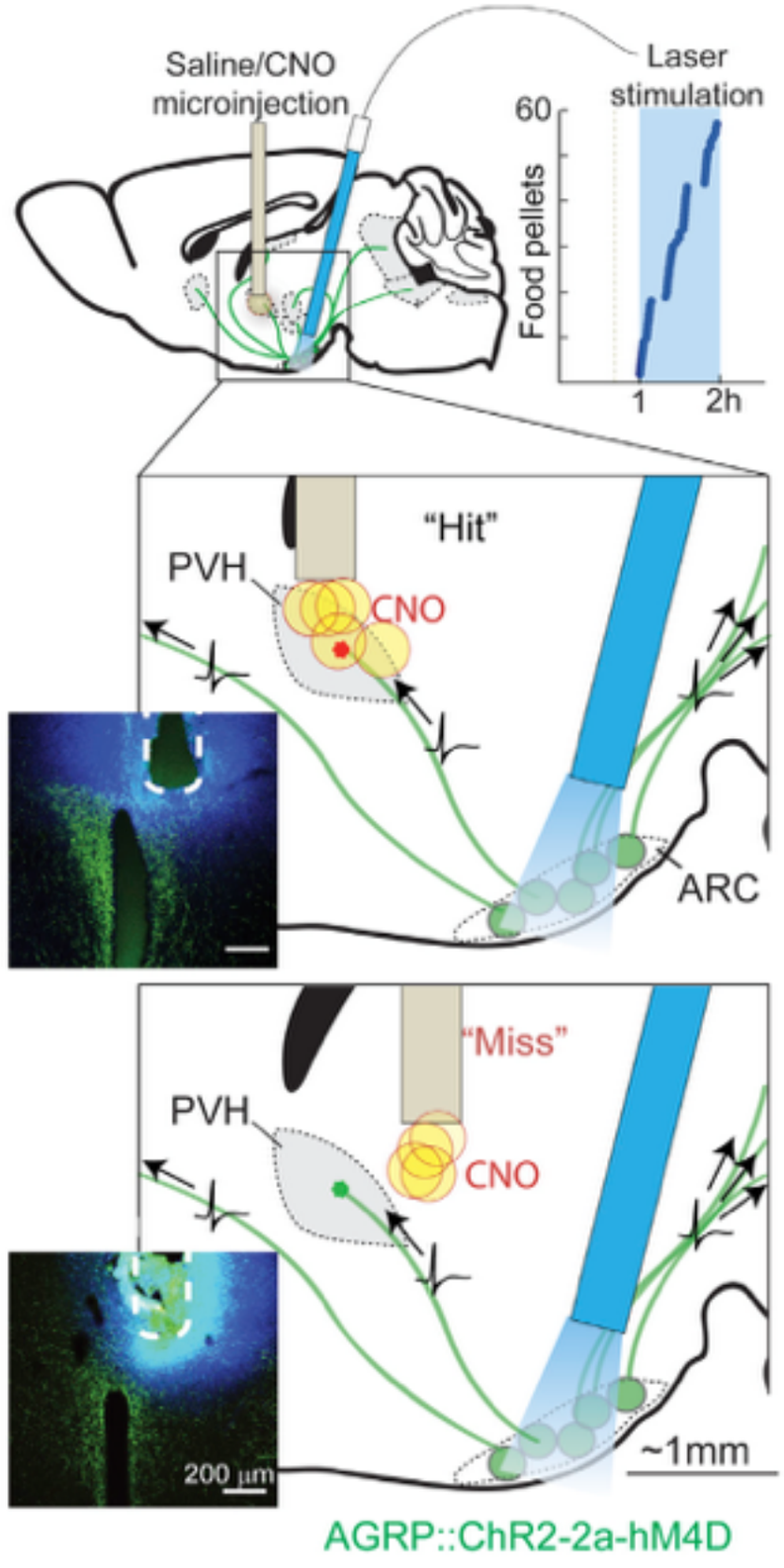
Neuron 82, 797–808, May 21, 2014

Chemogenetic Synaptic Silencing of Neural Circuits Localizes a Hypothalamus → Midbrain Pathway for Feeding Behavior

Tevye J. Stachniak,[1,2] Anirvan Ghosh,[2,3] and Scott M. Sternson[1,*]



Chemogenetic control via G protein-coupled receptors



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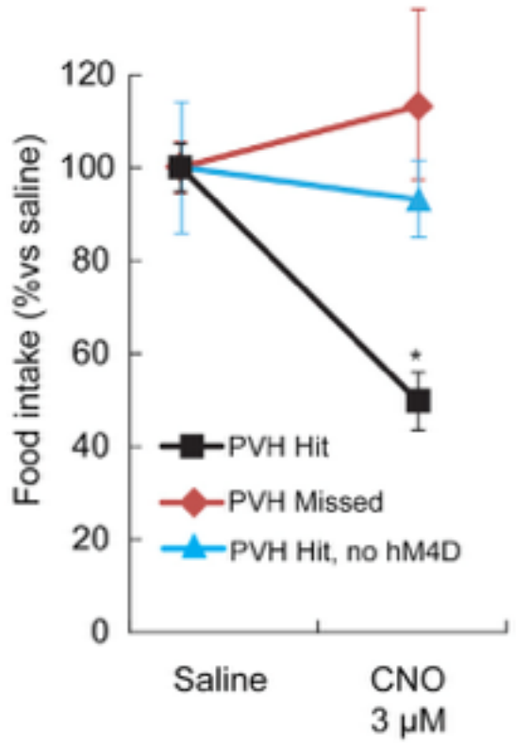
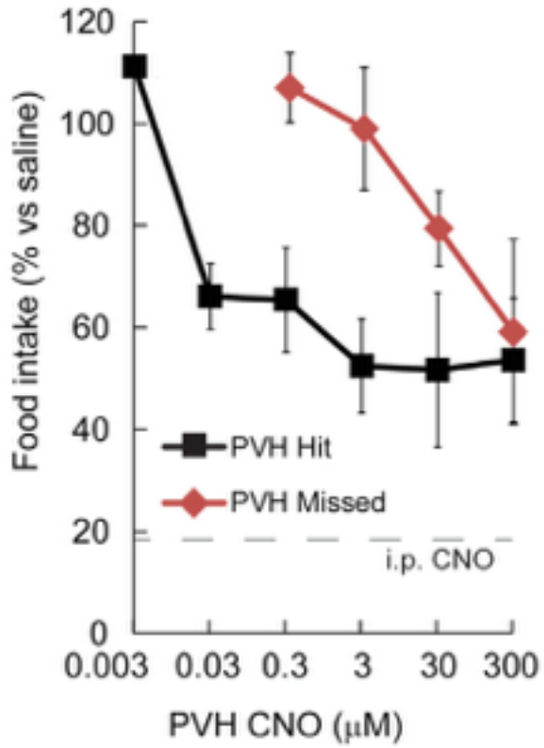
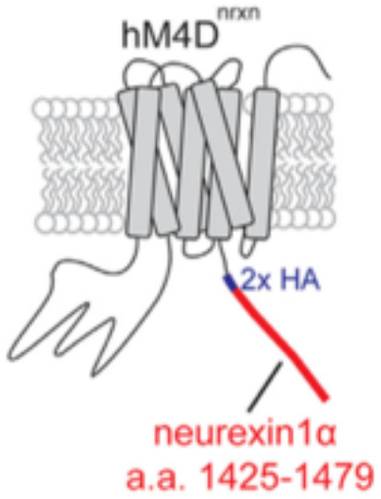
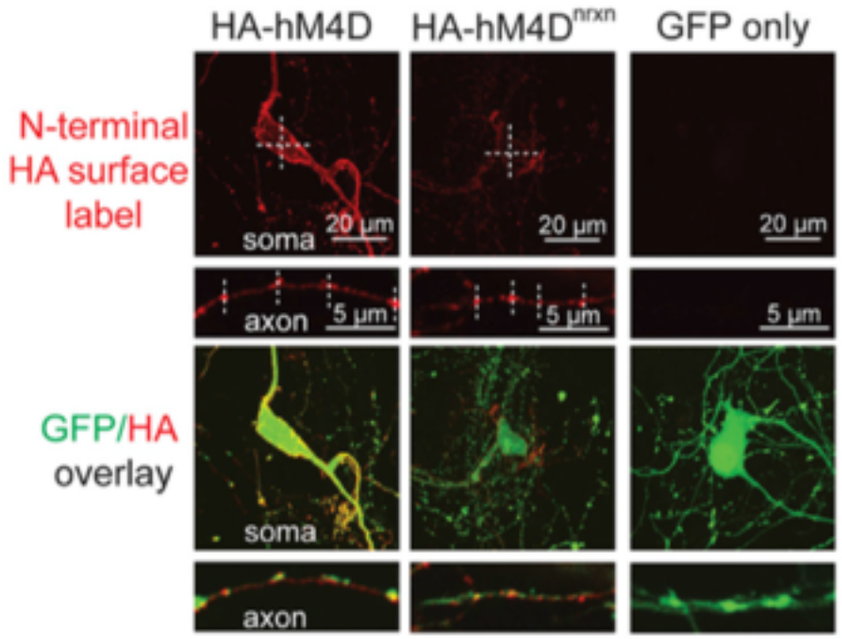
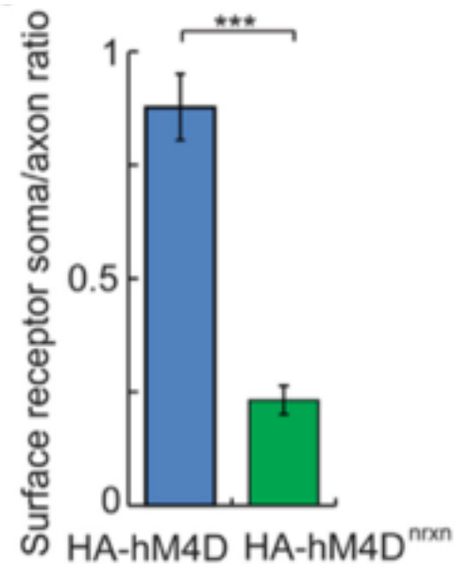


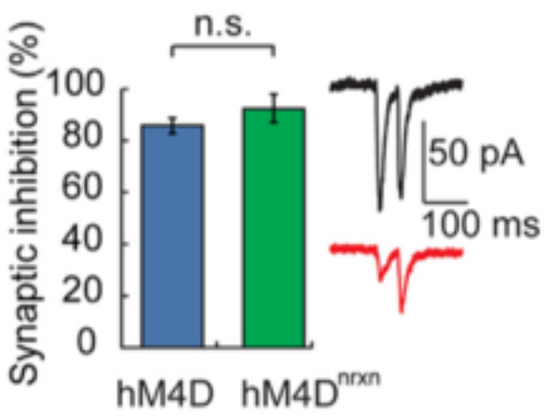


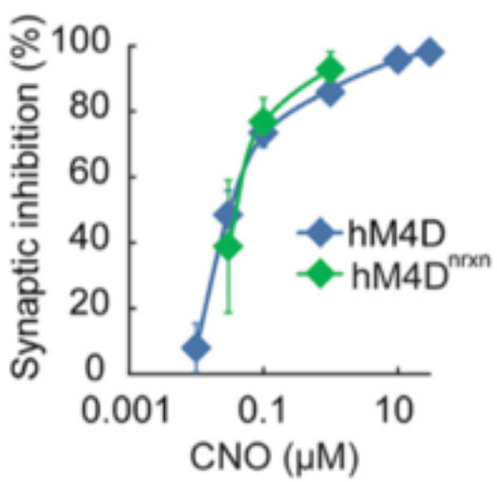
Chemogenetic control via G protein-coupled receptors

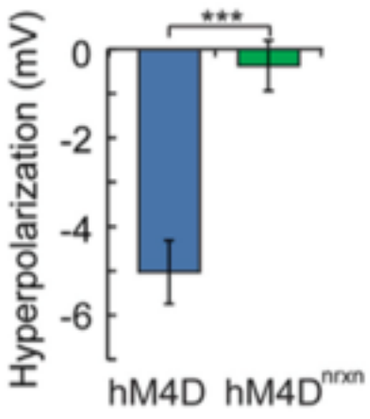


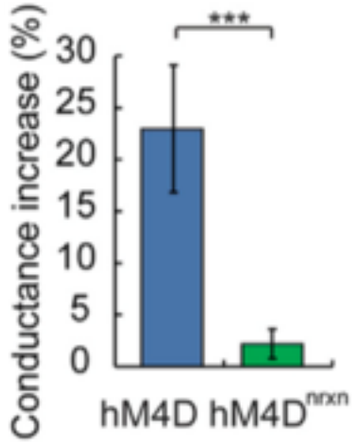




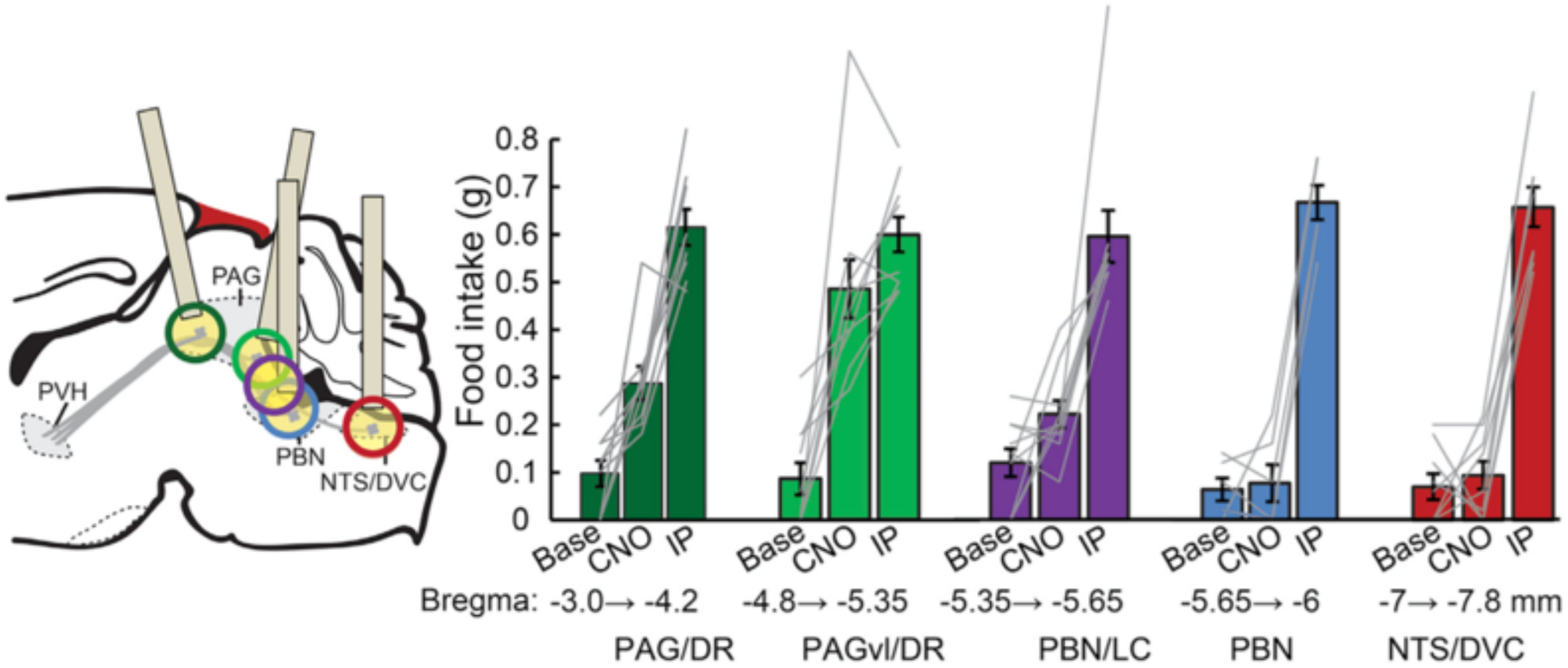








Chemogenetic control via G protein-coupled receptors

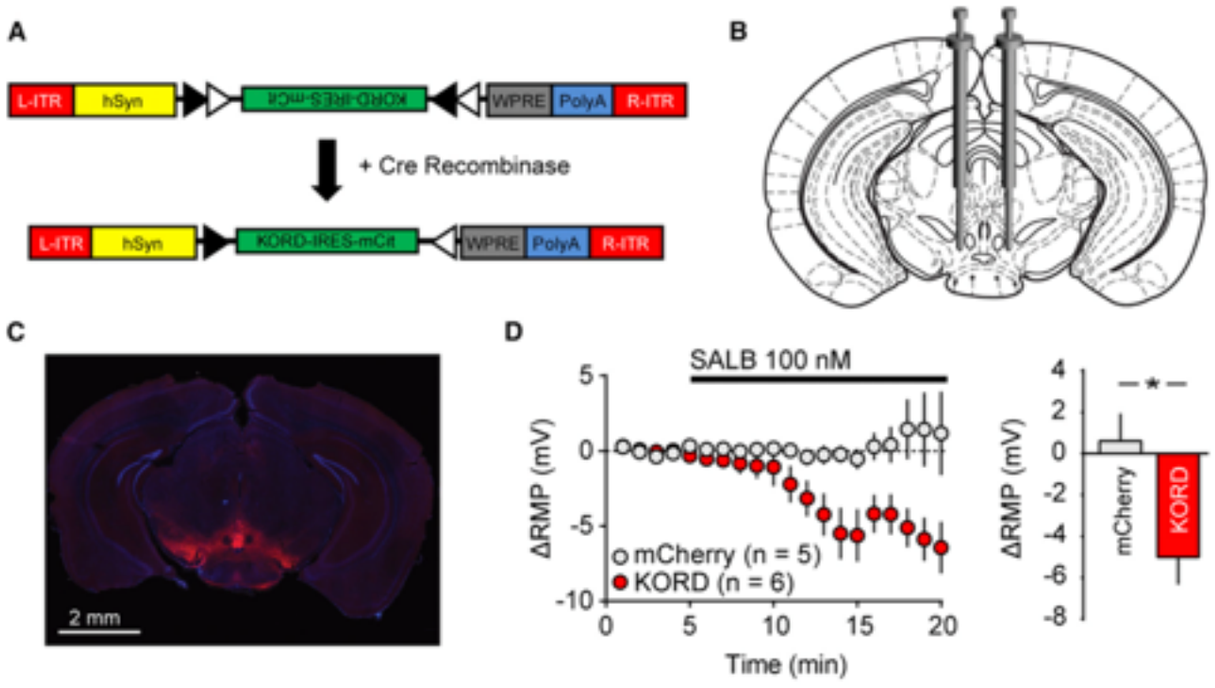


New inhibitory tools

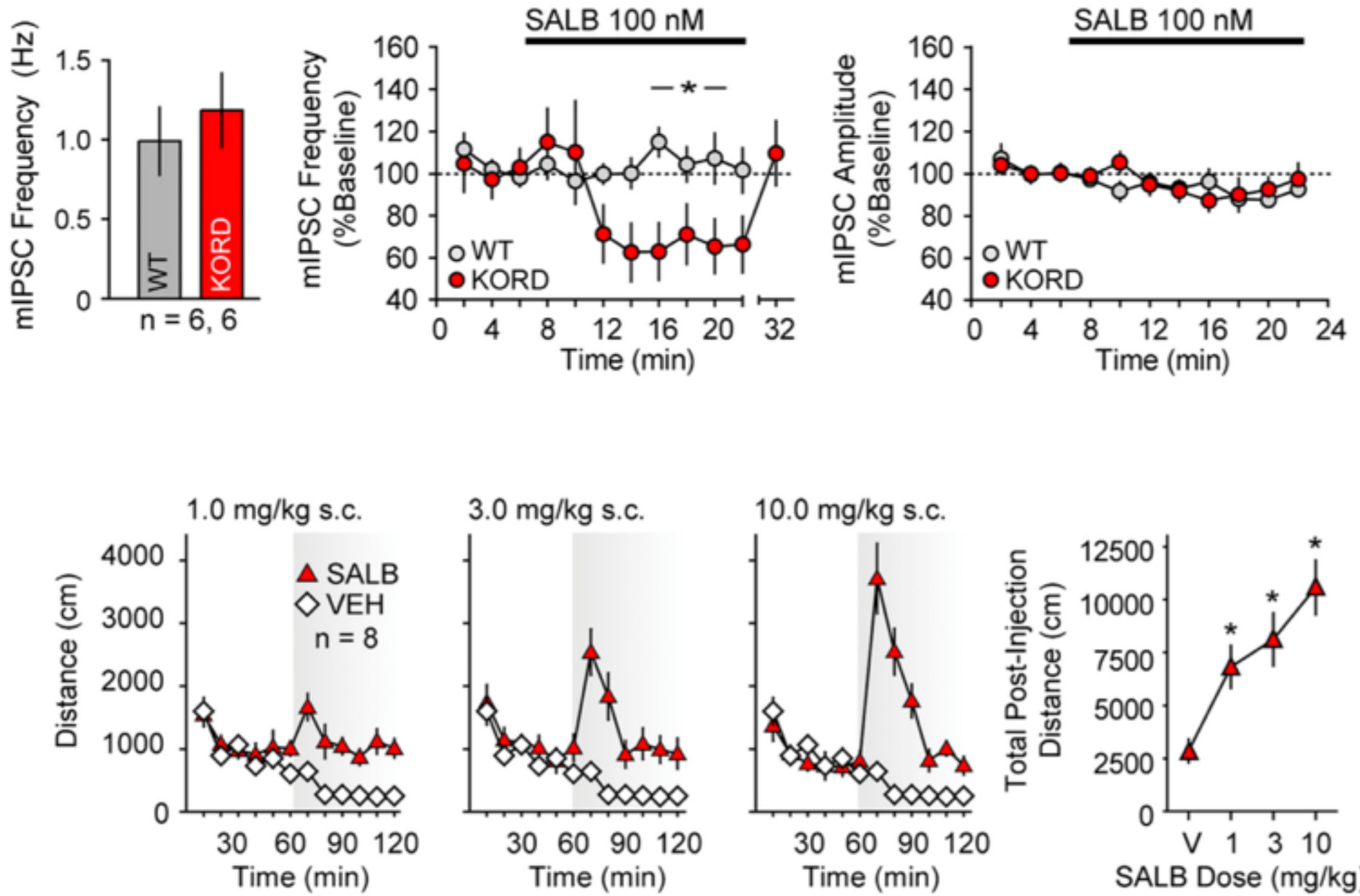
Neuron *86*, 936–946, May 20, 2015

A New DREADD Facilitates the Multiplexed Chemogenetic Interrogation of Behavior

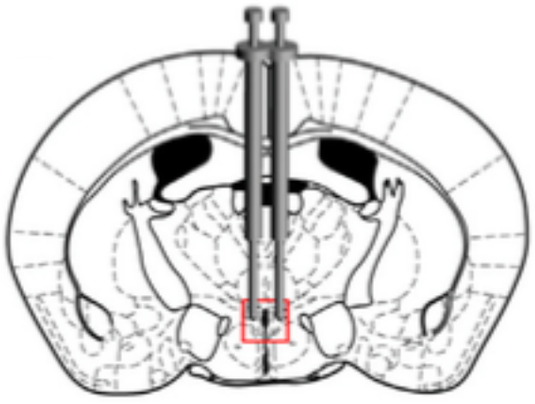
Eyal Vardy,[1,8] J. Elliott Robinson,[2,3,4,8] Chia Li,[5,6,8] Reid H.J. Olsen,[1,3] Jeffrey F. DiBerto,[2] Patrick M. Giguere,[1] Flori M. Sassano,[1] Xi-Ping Huang,[1] Hu Zhu,[1] Daniel J. Urban,[1] Kate L. White,[1] Joseph E. Rittiner,[3] Nicole A. Crowley,[1,3,4] Kristen E. Pleil,[1,3,4] Christopher M. Mazzone,[1,3,4] Philip D. Mosier,[7] Juan Song,[1,3] Thomas L. Kash,[1,3,4] C.J. Malanga,[2,3,4] Michael J. Krashes,[5,6,*] and Bryan L. Roth[1,3,*]

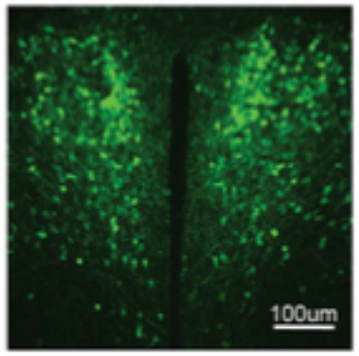


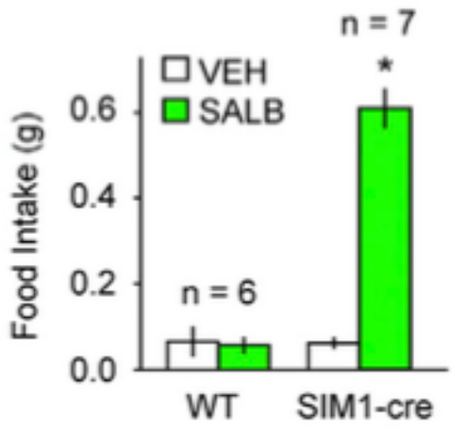
New inhibitory tools

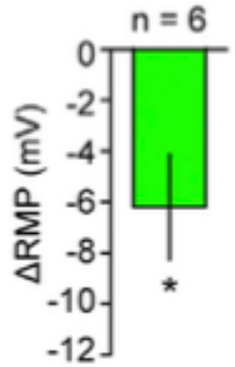


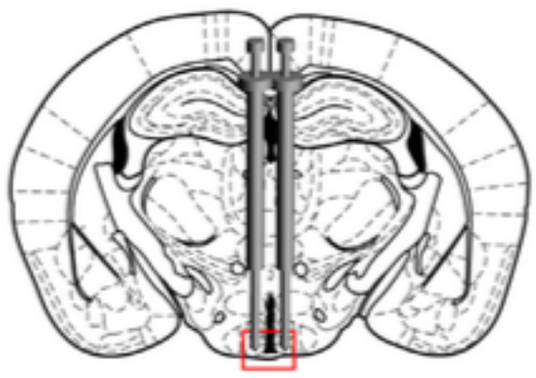
New inhibitory tools

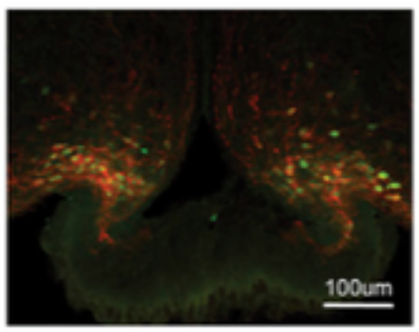


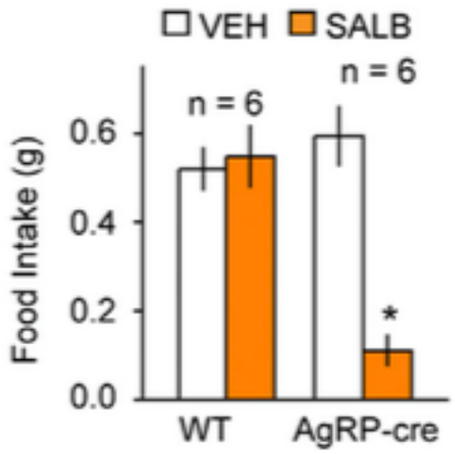


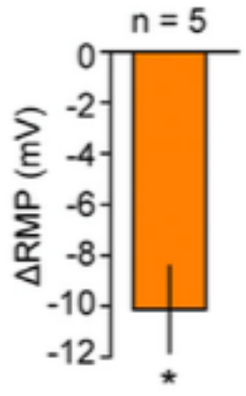




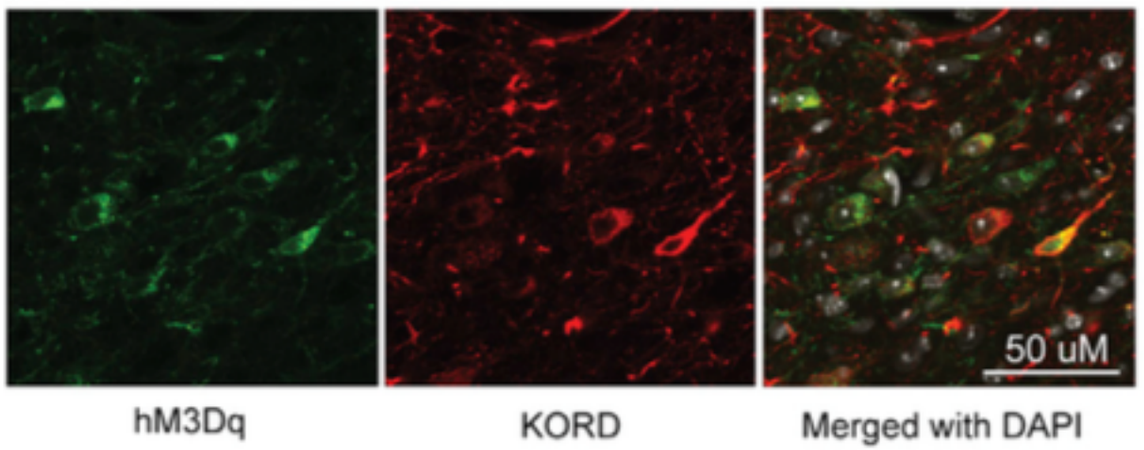


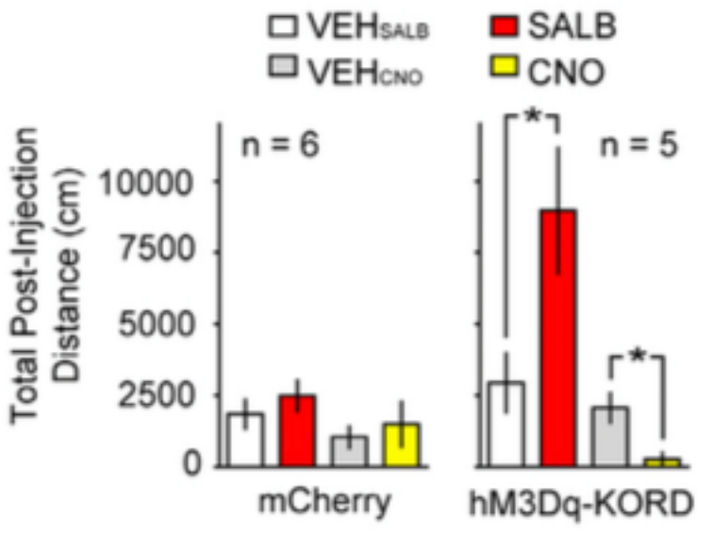


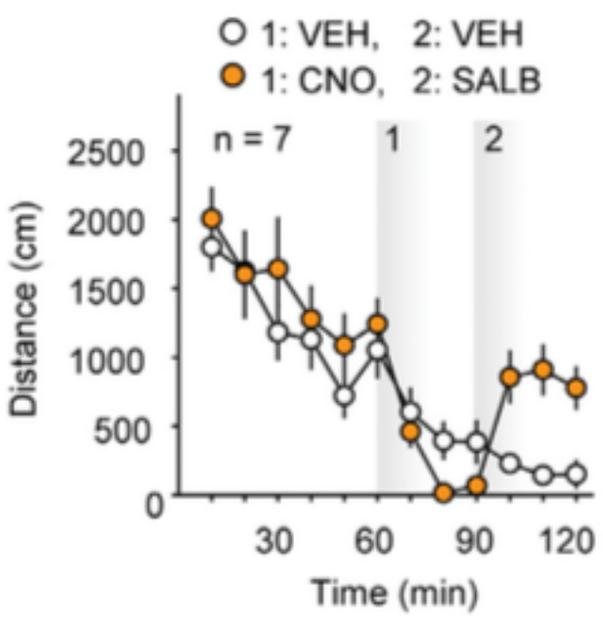


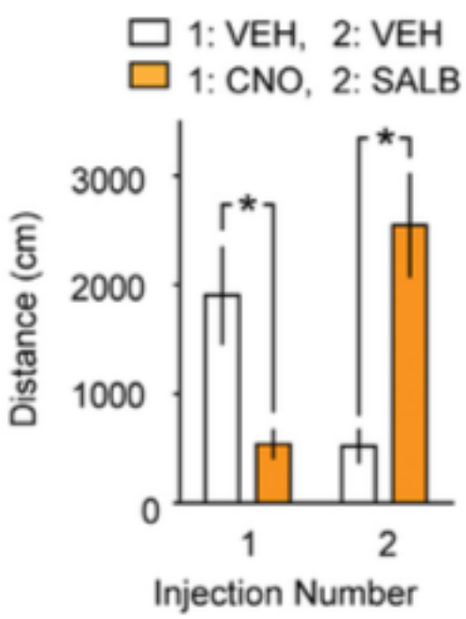


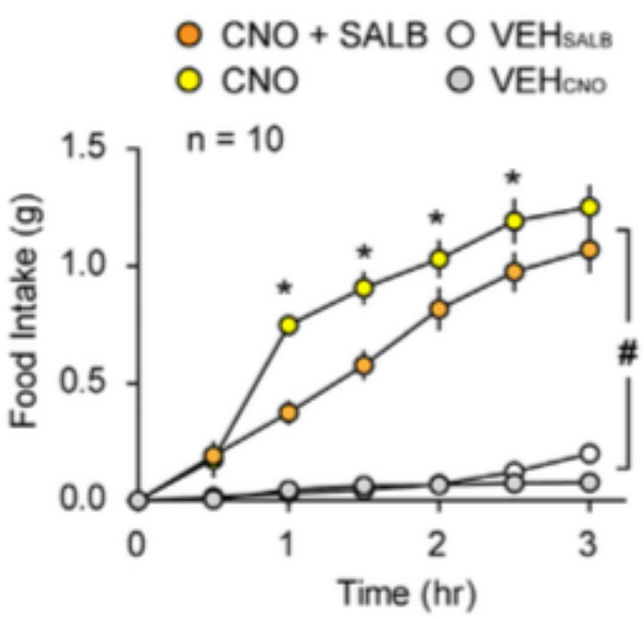
New inhibitory tools











Chemogenetic control via G protein-coupled receptors

Positive or neutral:

Minimal or no brain lesion

It can be used coupled to a variety of mouse models (no need to use on a KO background)

Reversible

Theoretically, allows developmental studies

Can be multiplexed

Can be used to study specific signaling modalities in different cell populations (not only excitable cells)

Negative:

Temporal resolution is not good:

Variable latency

Lasts several hours

CNO cannot be used in models that can metabolize to clozapine

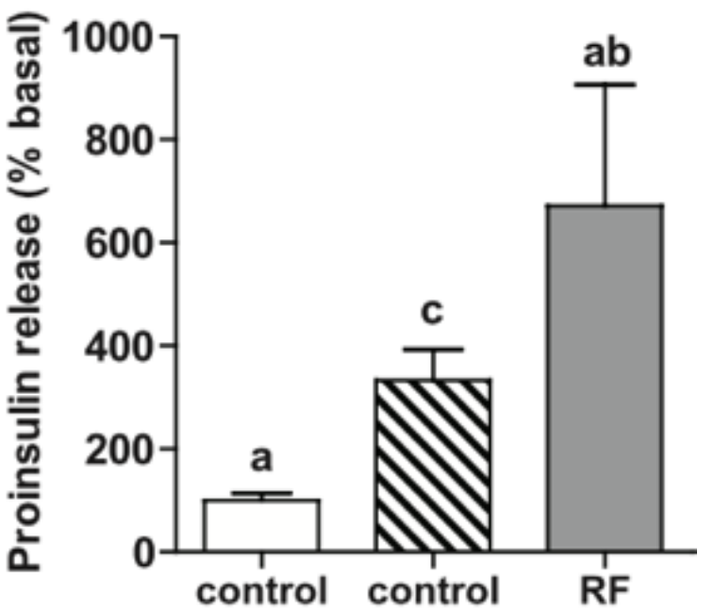
DREADDs impact cell signaling and might have broad implications for cell physiology beyond changes in activity (e.g., arrestin signaling)

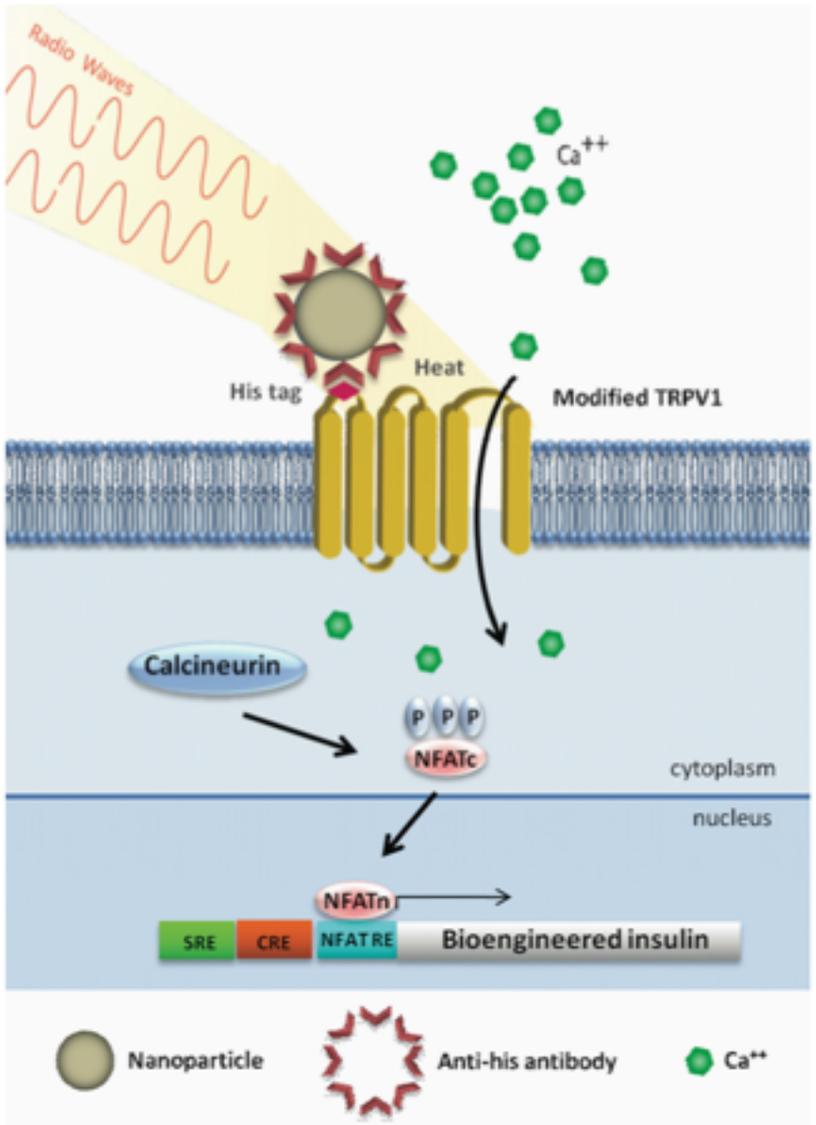
Beyond chemogenetic tools

4 MAY 2012 VOL 336 **SCIENCE** www.sciencemag.org

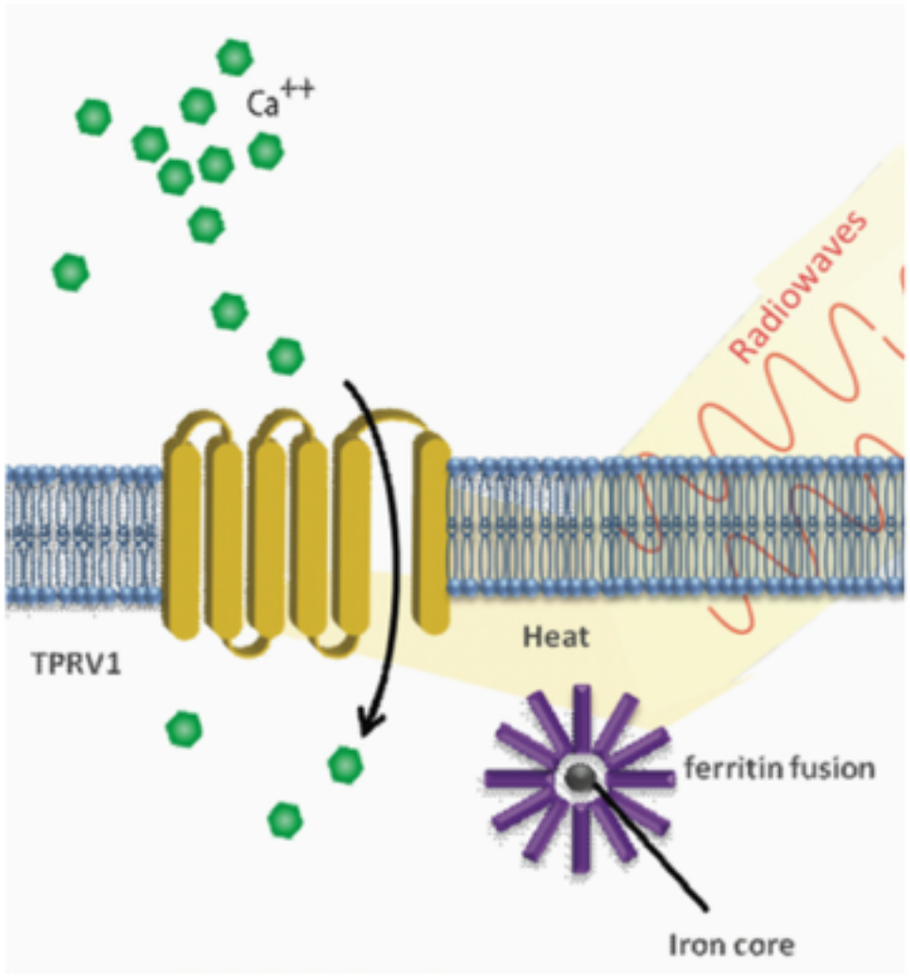
Radio-Wave Heating of Iron Oxide Nanoparticles Can Regulate Plasma Glucose in Mice

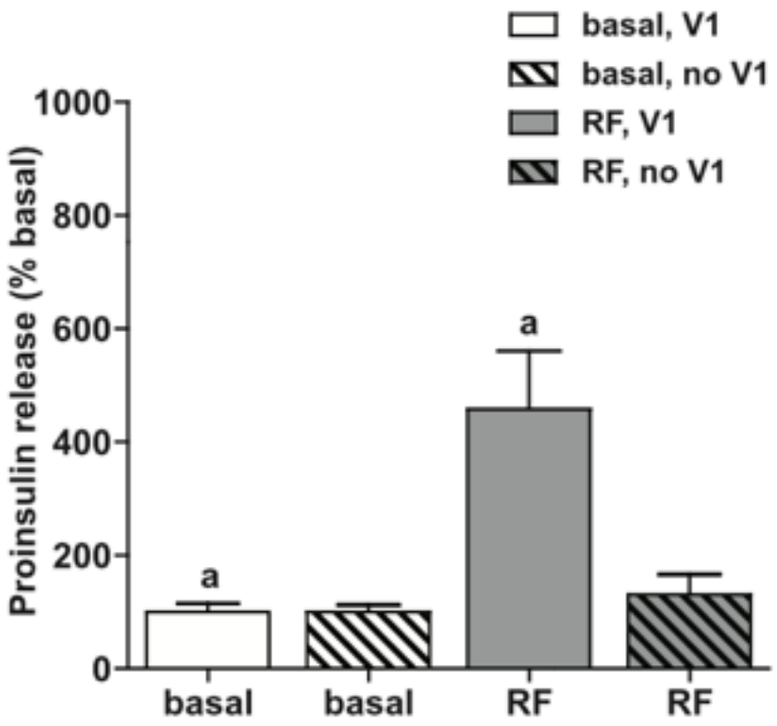
Sarah A. Stanley,[1] Jennifer E. Gagner,[2] Shadi Damanpour,[1] Mitsukuni Yoshida,[3] Jonathan S. Dordick,[4] Jeffrey M. Friedman[1,5]*





Beyond chemogenetic tools





Beyond chemogenetic tools

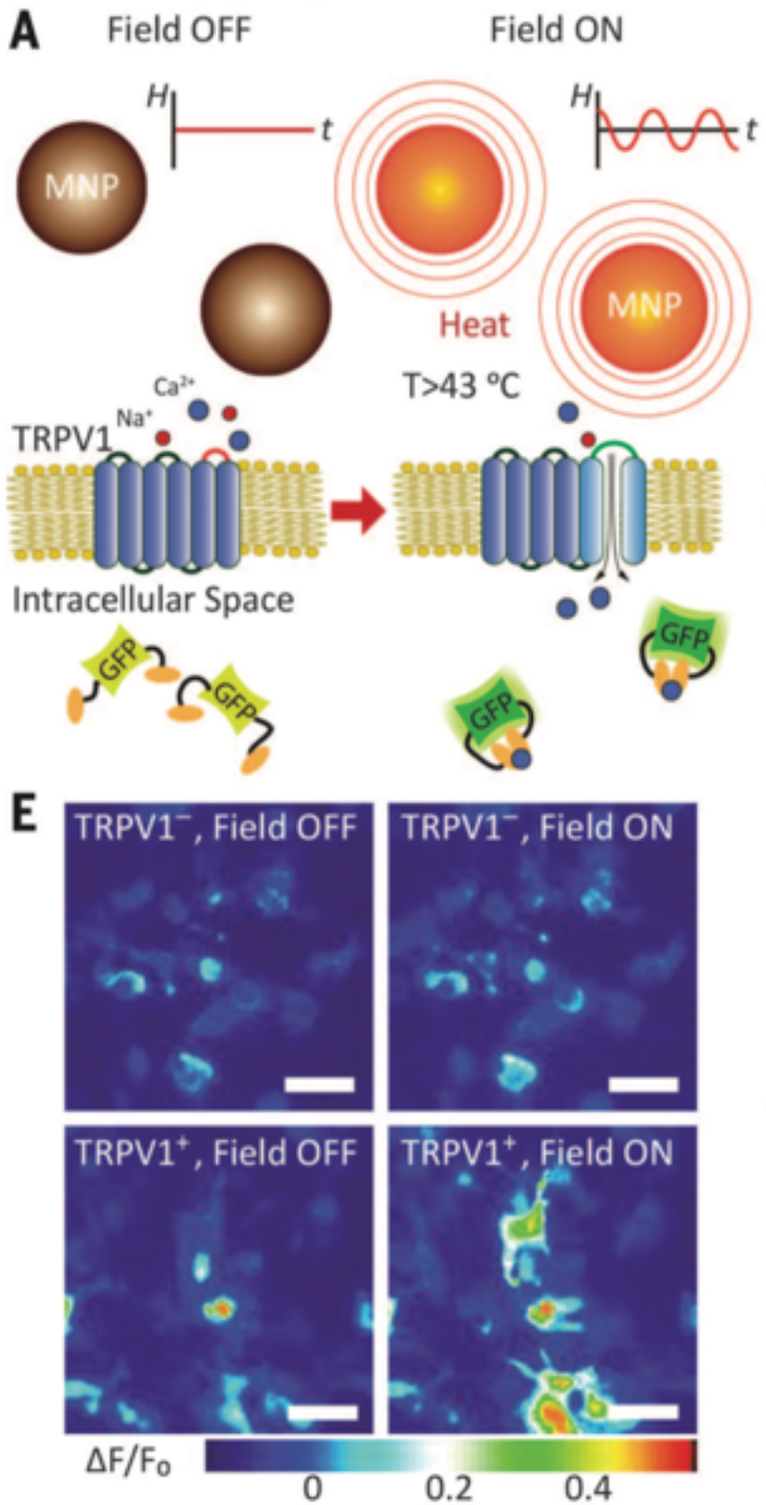
NEUROTECHNIQUES

Wireless magnetothermal deep brain stimulation

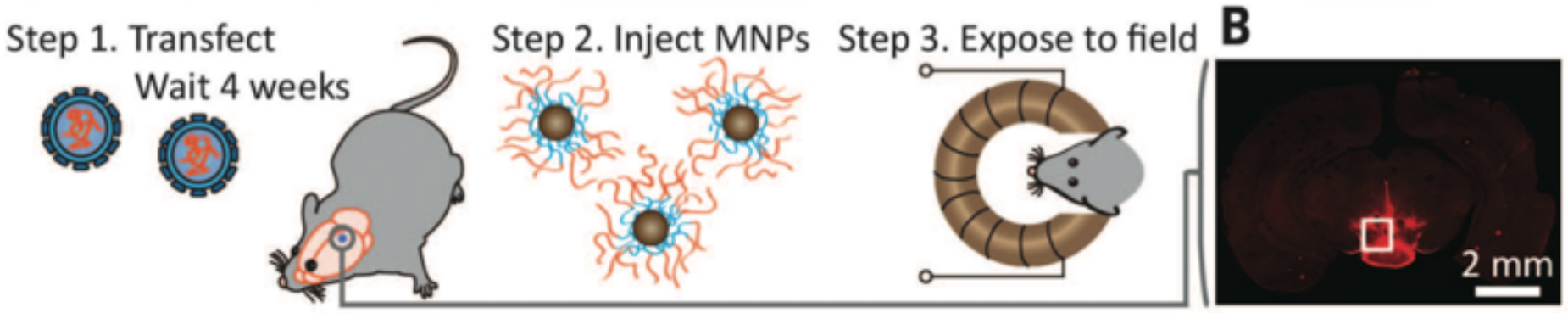
Ritchie Chen,[1,2] Gabriela Romero,[2] Michael G. Christiansen,[1,2]
Alan Mohr,[3] Polina Anikeeva[1,2]*

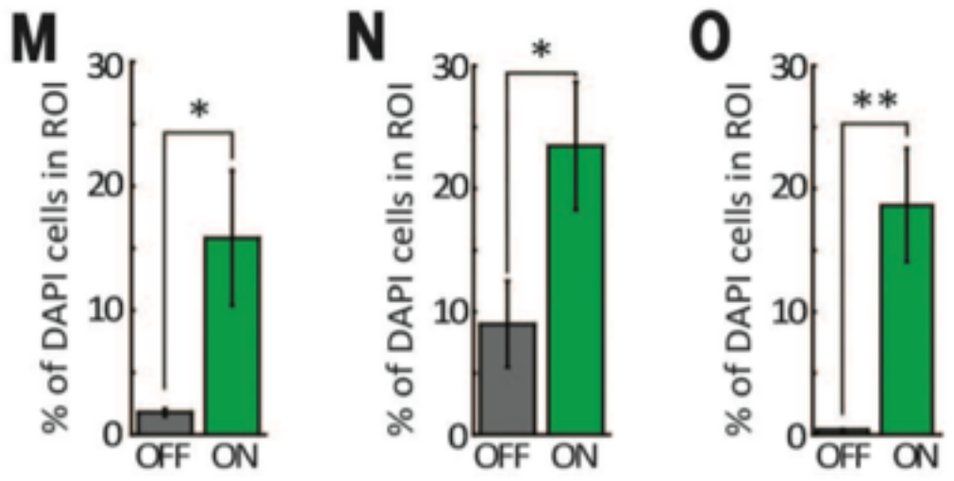
SCIENCE sciencemag.org

27 MARCH 2015 • VOL 347 ISSUE 6229



Beyond chemogenetic tools



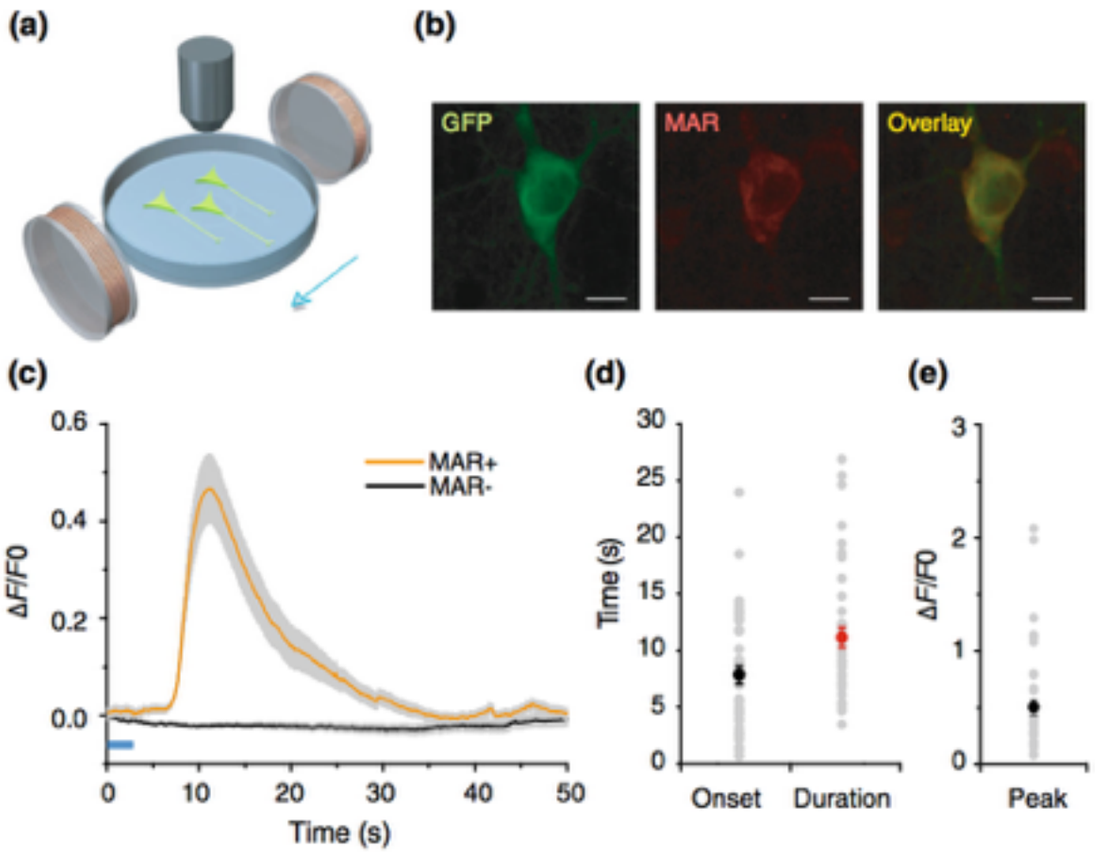


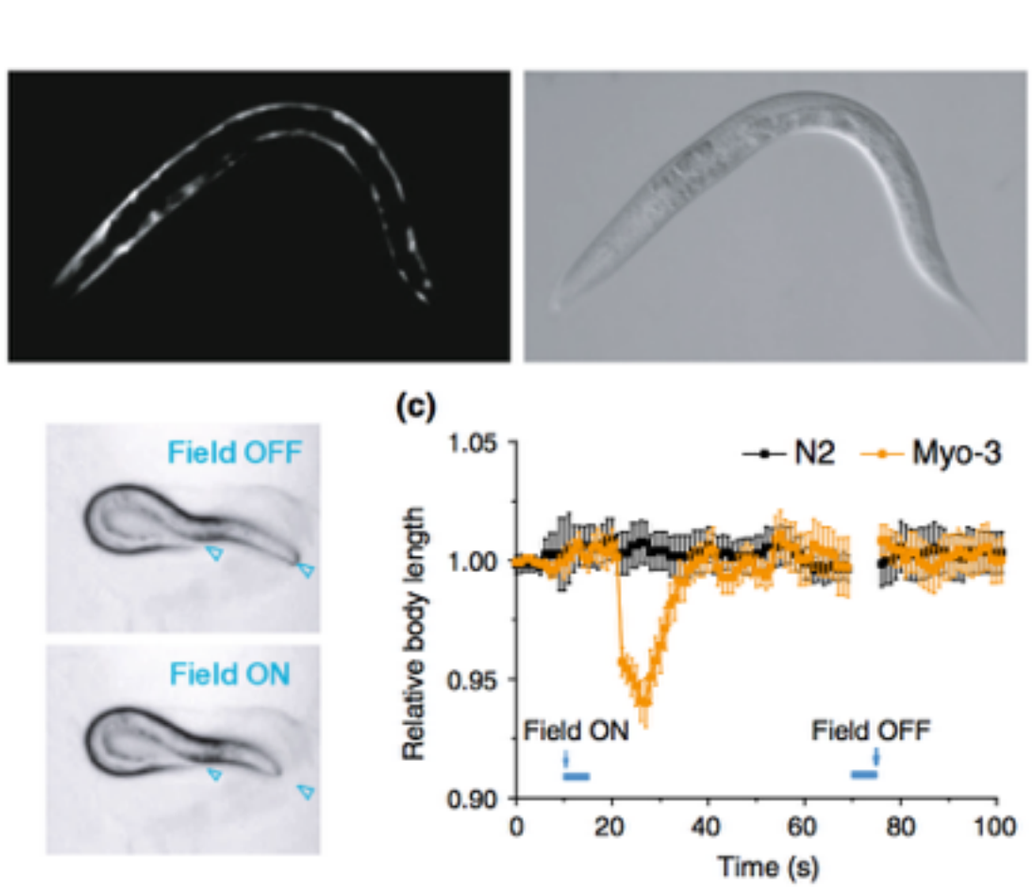
Magnetogenetics

Sci. Bull.
DOI 10.1007/s11434-015-0902-0

Magnetogenetics: remote non-invasive magnetic activation of neuronal activity with a magnetoreceptor

Xiaoyang Long · Jing Ye · Di Zhao · Sheng-Jia Zhang





Conclusions

Together with optogenetics, chemogenetic tools provide the investigator with a toolbox to manipulate neuronal function and study physiology and behavior.

All tools have pros and cons; controls are important to add biological validity to experimental data.

With all tools now available, there is a fertile soil for conceptually novel ideas to change our view on how the brain works.

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- Whitehall Foundation Research Grant
- Yale Center for Clinical Investigation Scholar Award
- NARSAD Young Investigator, Brain & Behavior Research Foundation
- Yale School of Medicine
- CAPES (Brazil)
- CNPq (Brazil)

I declare to have no conflicts of interest.

Thank you.

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