

Chemogenetic tools to interrogate brain functions in health and disease

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- Optogenetics (advantages and drawbacks)
- **DREADDs (Designer Receptors Exclusively Activated by a Designer Drug, Chemogenetics using GPCRs)**
- PSAM and PSEM (Chemogenetics using ion channels)
- Luminopsins (Converging chemogenetics and optogenetics)

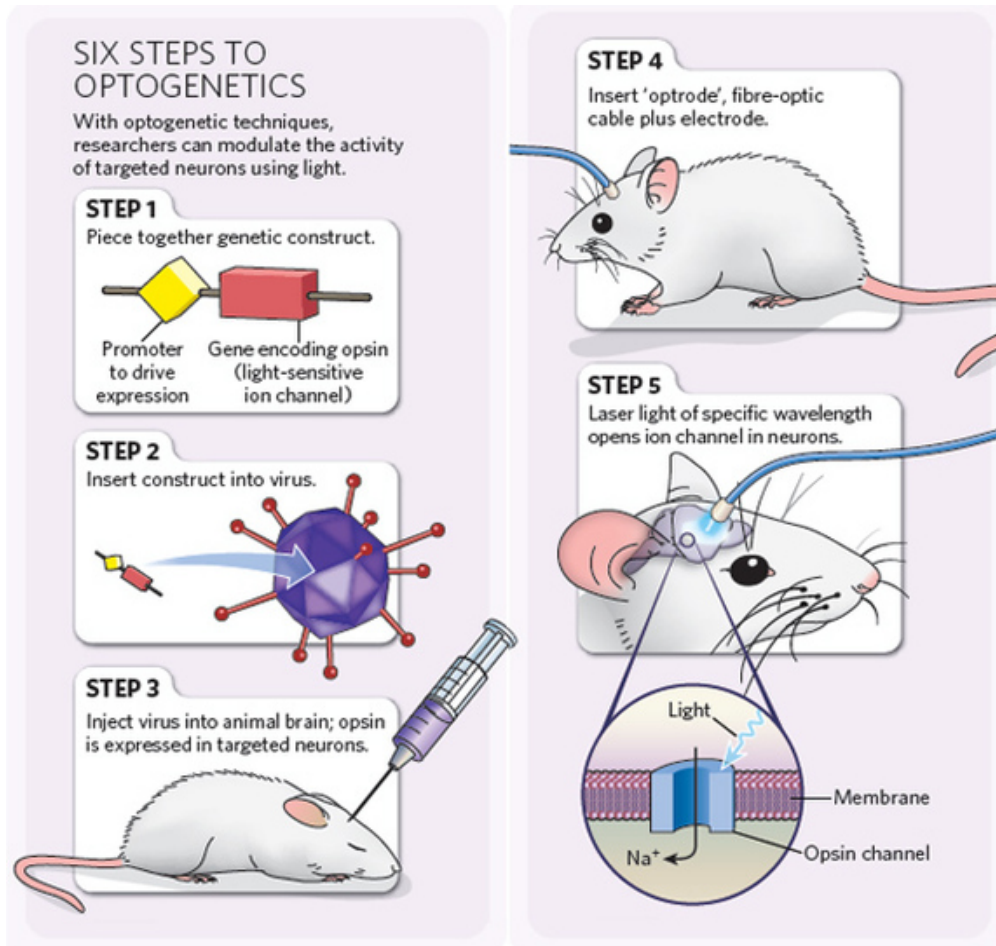
The impact of molecular biology on neuroscience

Francis Crick, OM FRS

The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA

A major first step, then, is to identify the many different types of neuron existing in the cerebral cortex and other parts of the brain. One of the next requirements (as discussed above) is to be able to turn the firing of one or more types of neuron on and off in the alert animal in a rapid manner. The ideal signal would be light, probably at an infrared wavelength to allow the light to penetrate far enough. This seems rather far-fetched but it is conceivable that molecular biologists could engineer a particular cell type to be sensitive to light in this way.

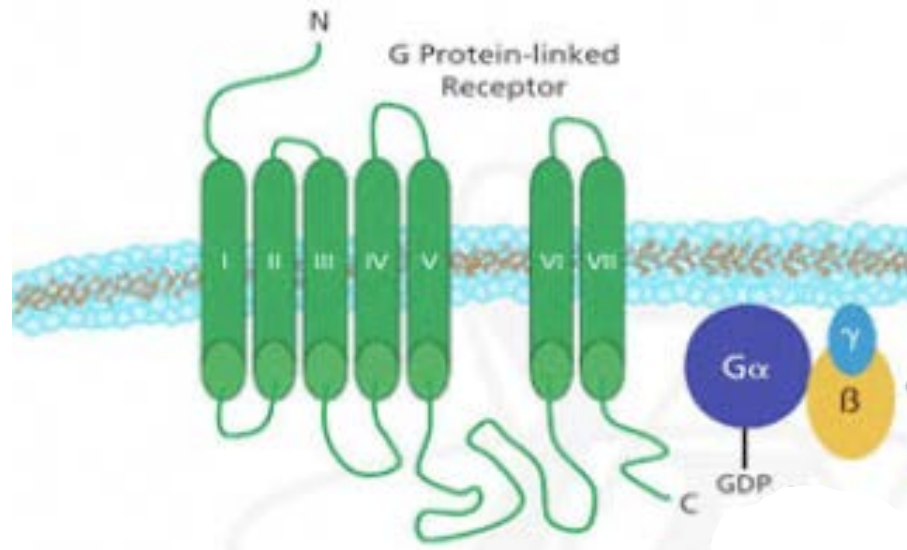
Optogenetics and its drawbacks



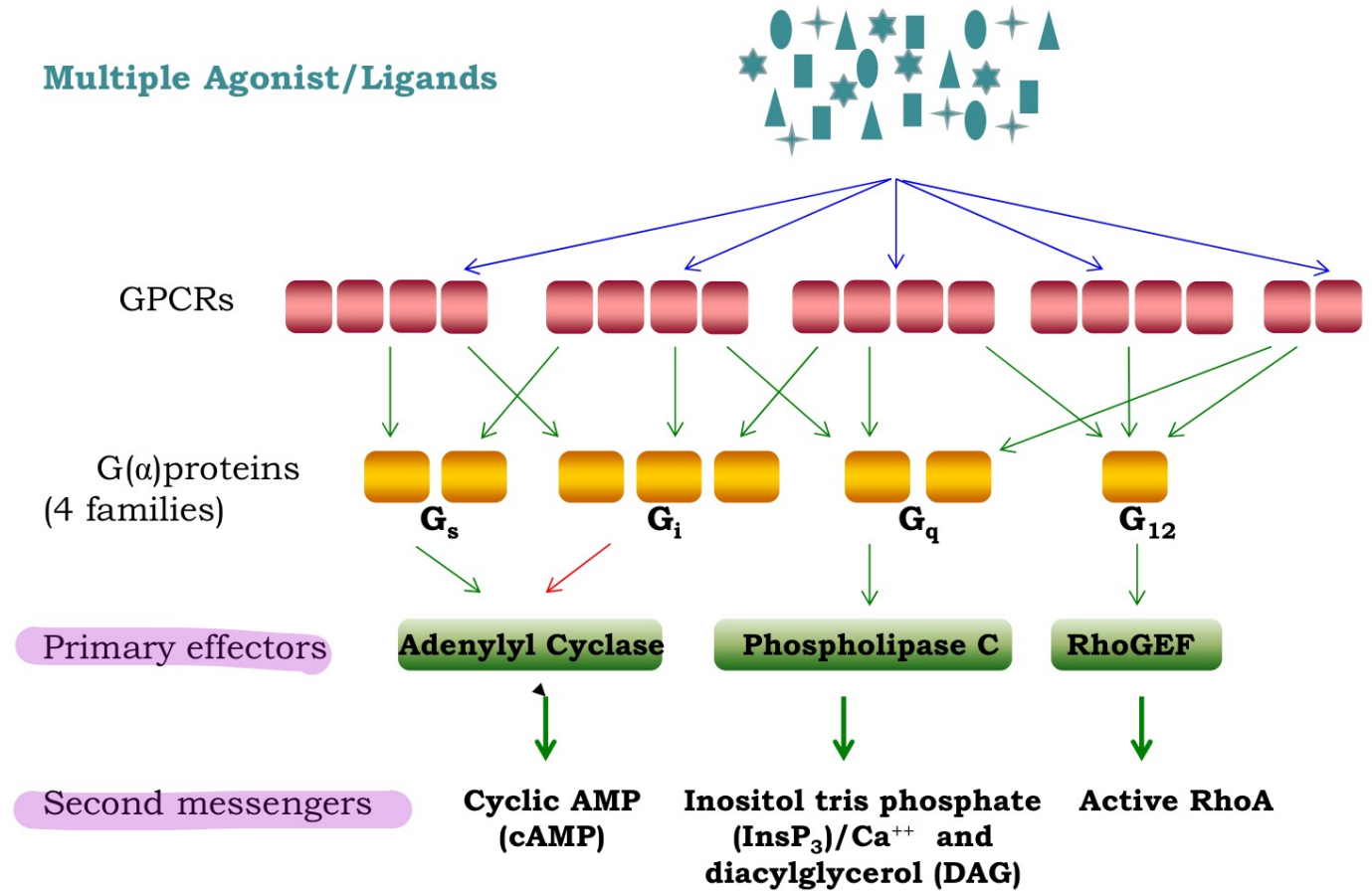
- Technically complex
- Expensive
- Invasive
- Not suitable for non-excitable cells
- Not suitable for long-term study
- Too local for some applications

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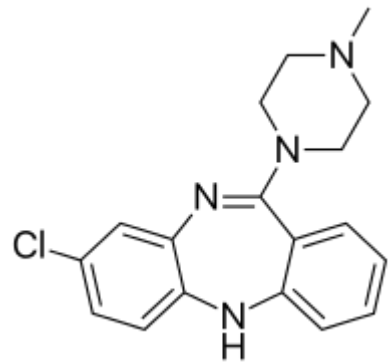
G protein coupled receptor signaling



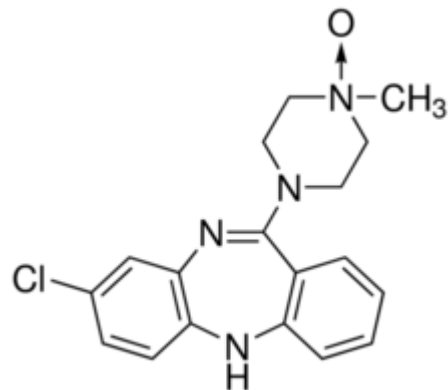
Multiple Agonist/Ligands



Clozapine N-oxide as a good candidate ligand



Clozapine



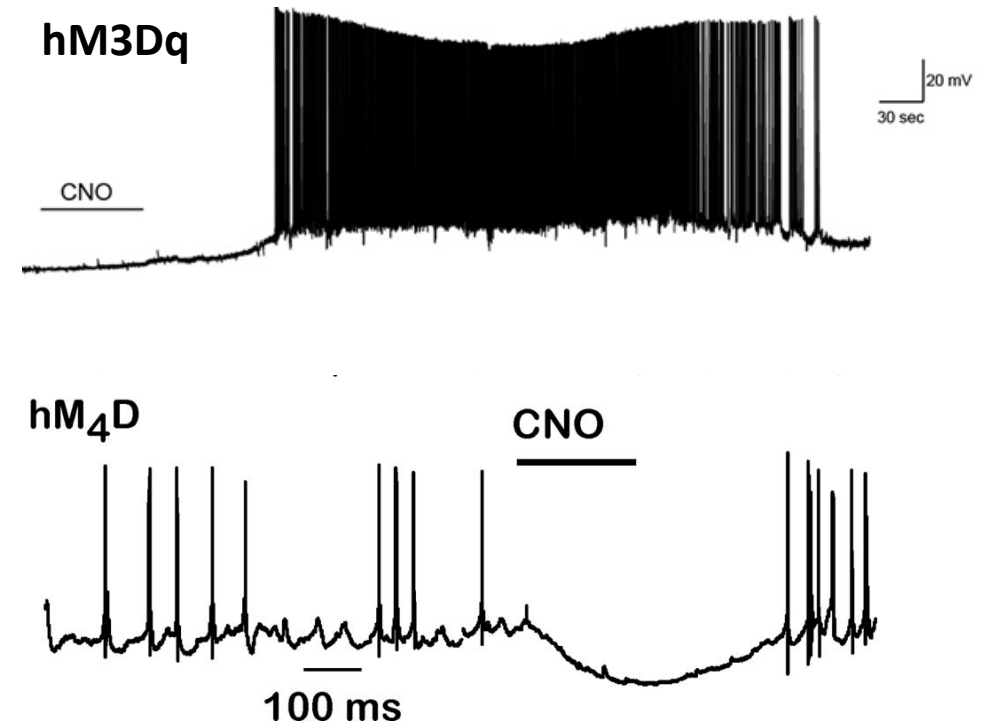
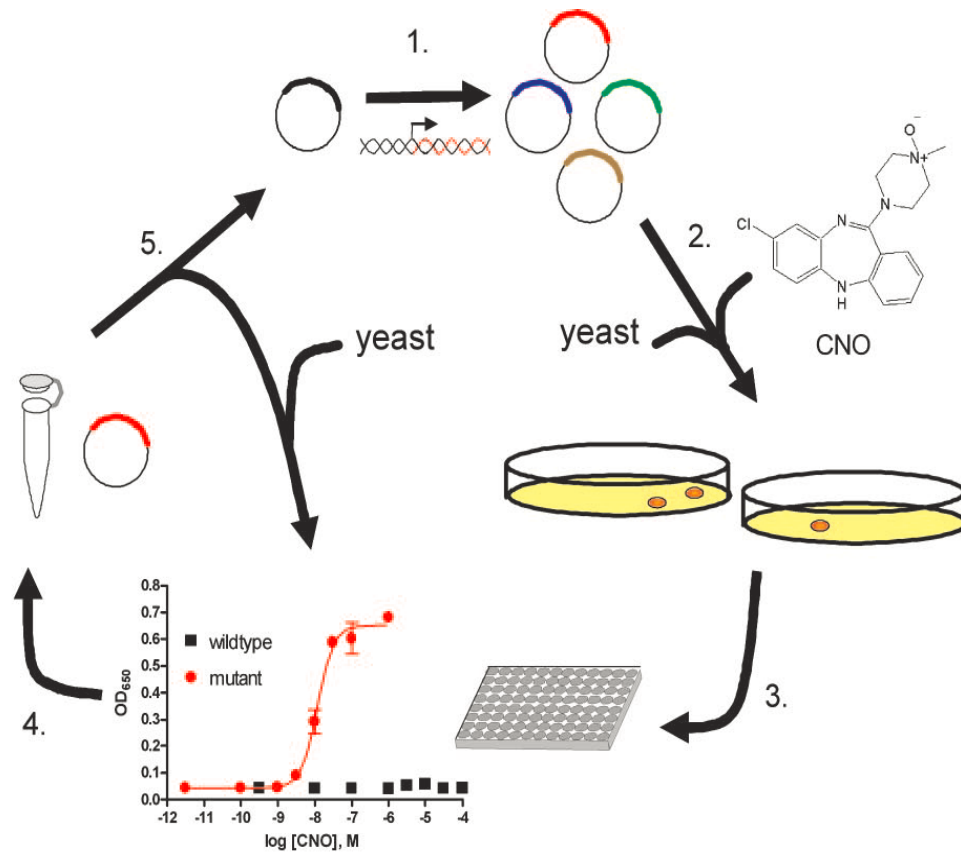
Clozapine N-oxide

- CNO is highly bioavailable and safe in rodents and humans
- CNO is a pharmacologically inert molecule lacking appreciable affinity for endogenous receptors
- its parent compound, clozapine, has high affinity to muscarinic receptors

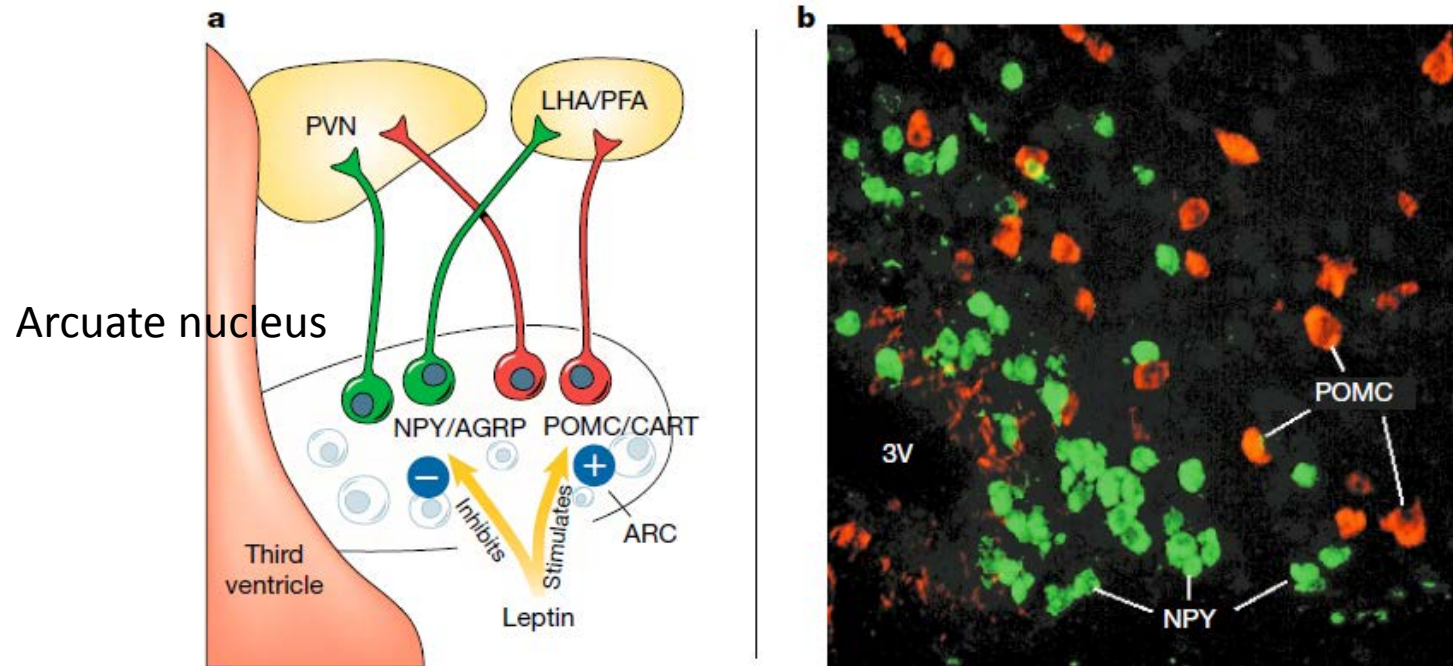
Evolving the lock to fit the key (molecular evolution of muscarinic receptors)

DREADDs (Designer Receptors Exclusively Activated by a Designer Drug)

A



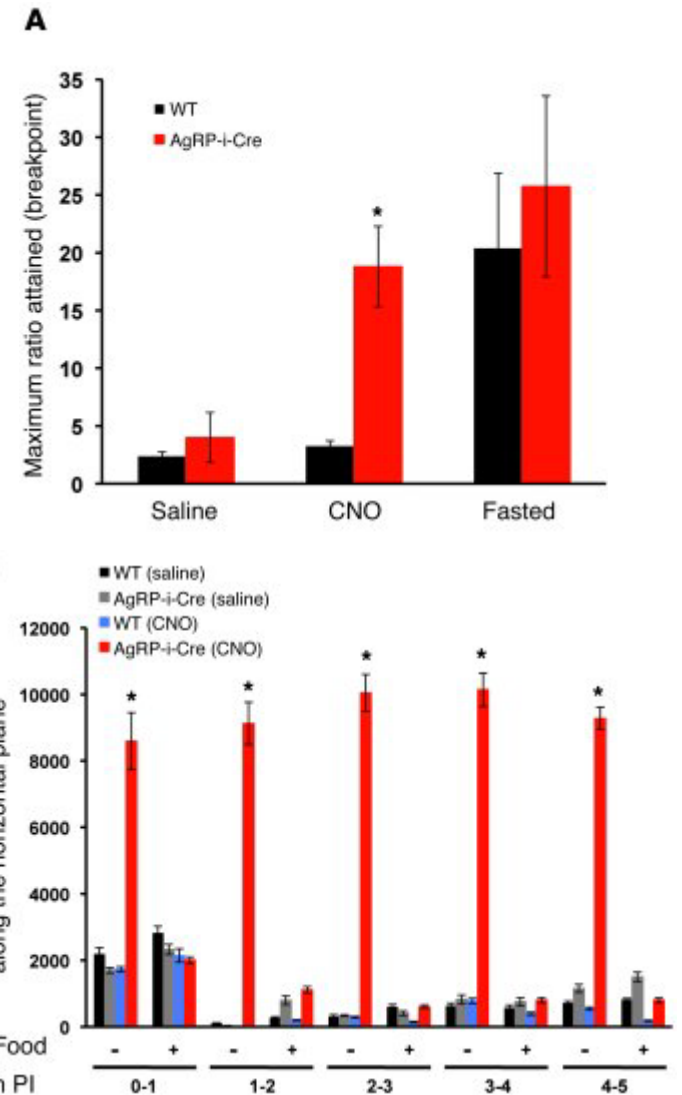
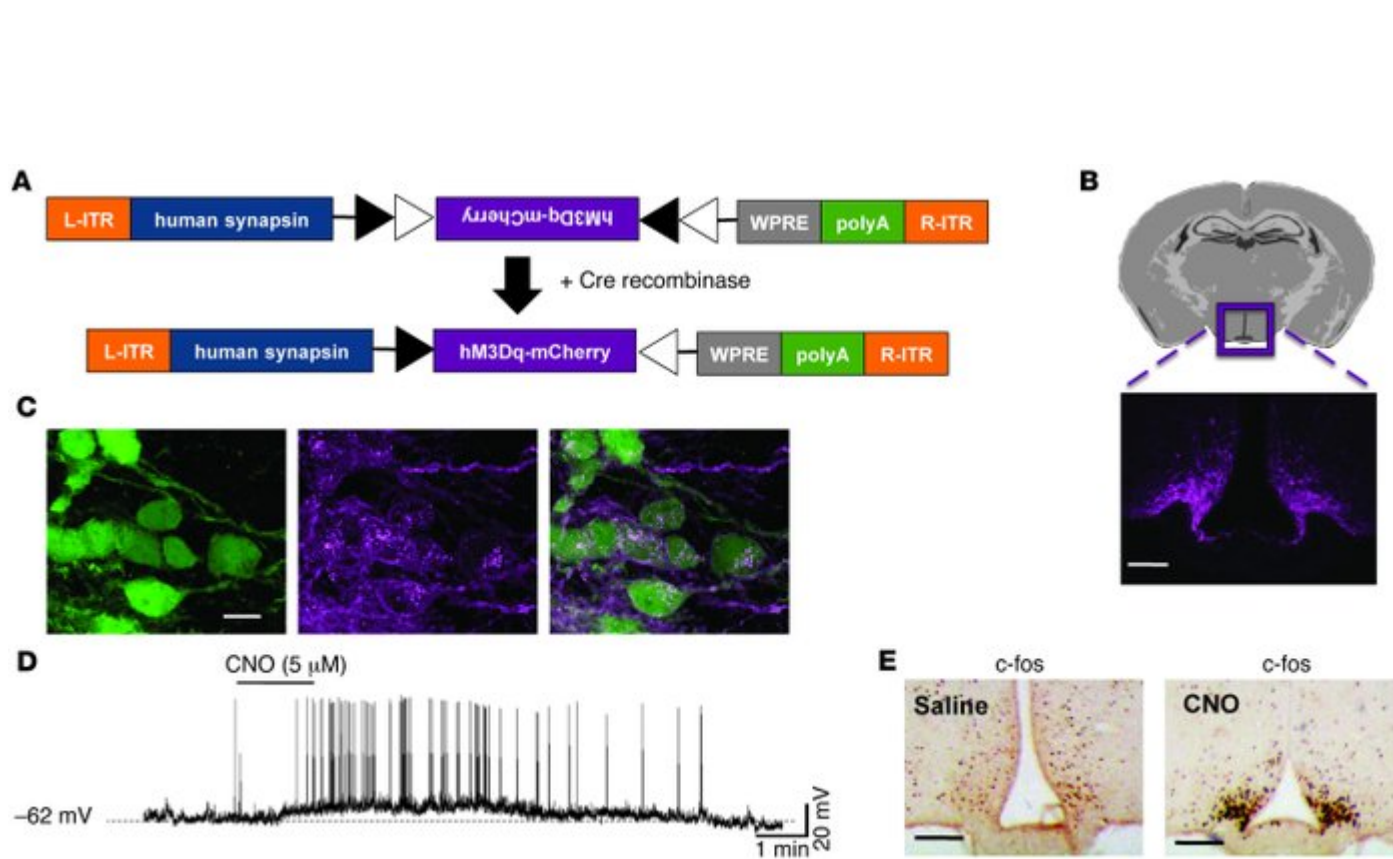
Neural basis of feeding



Central nervous system control of food intake, 2000, Nature

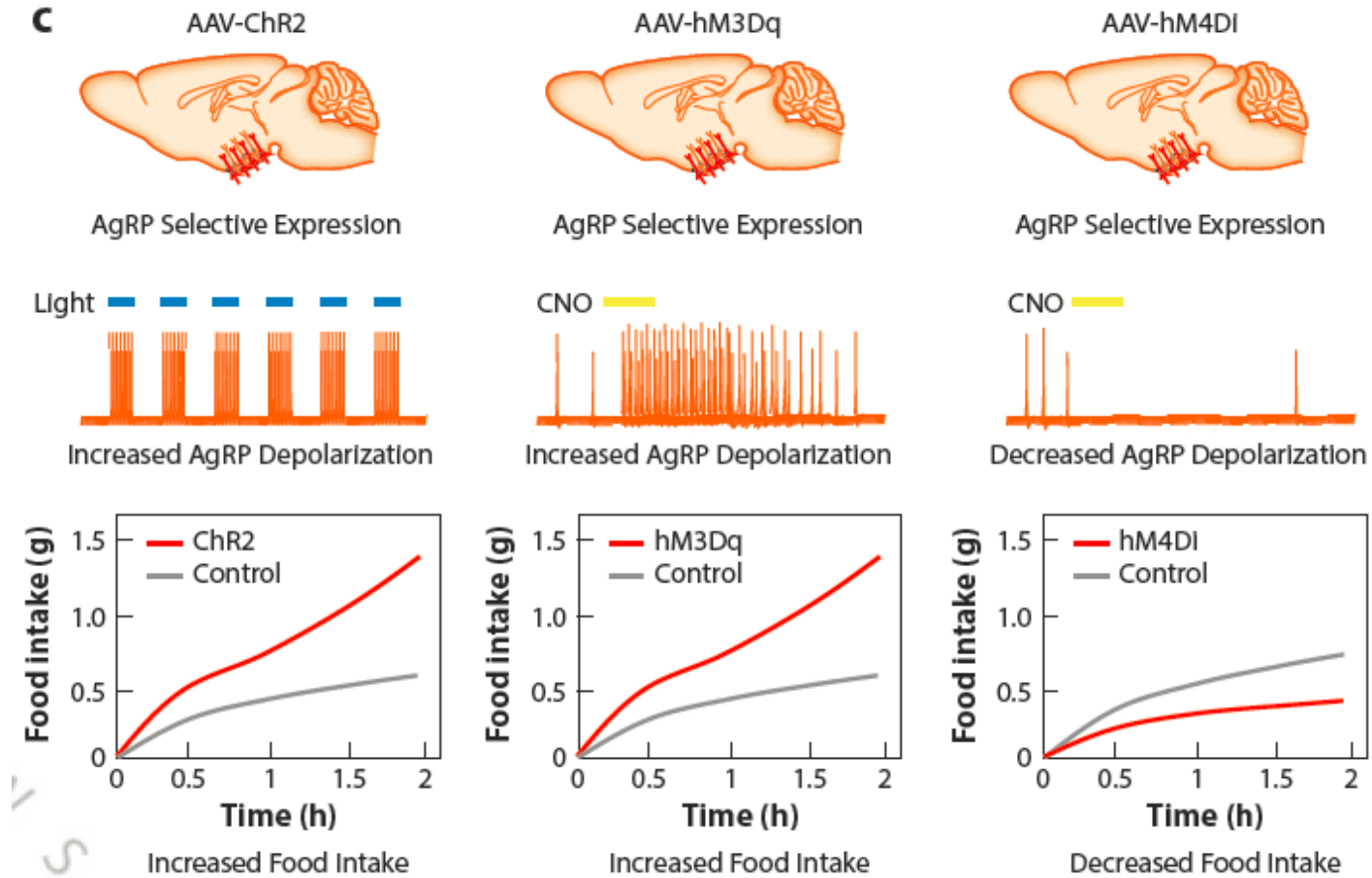
Michael W. Schwartz, Stephen C. Woods, Daniel Porte, Randy J. Seeley & Denis G. Baskin

Modulation of behaviors by DREADDs in living animals

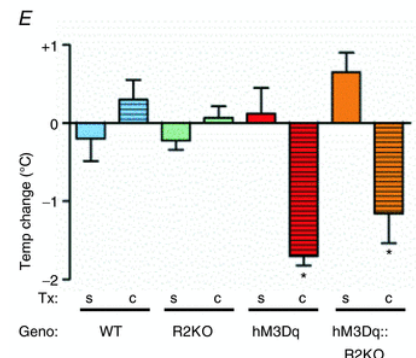
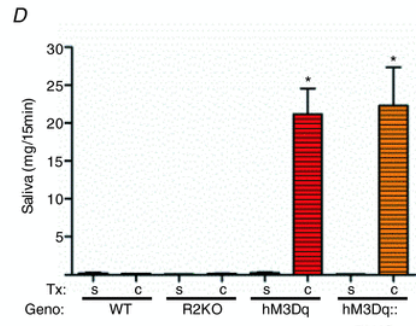
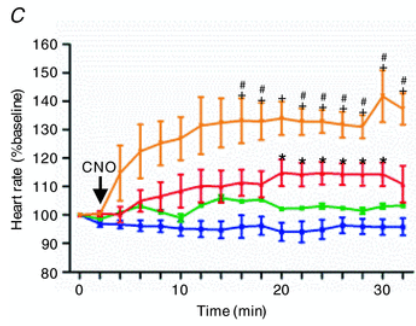
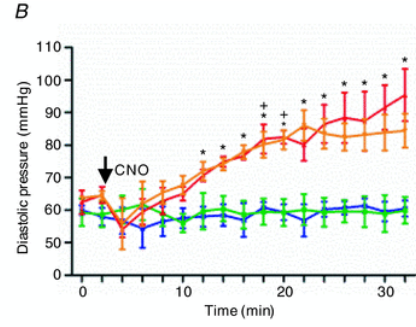
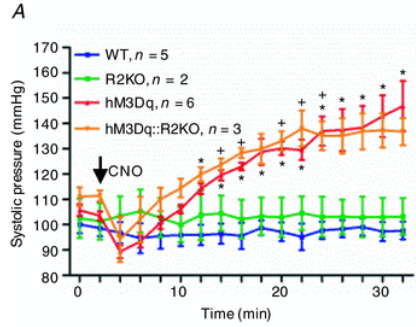
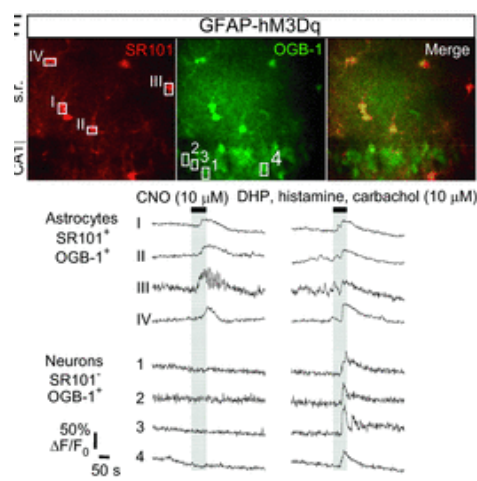


Michael J. Krashes, and Bradford B. Lowell et al., 2011, J Clin Invest.

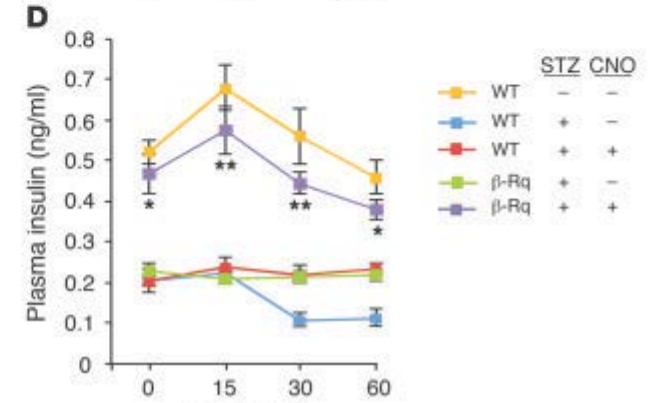
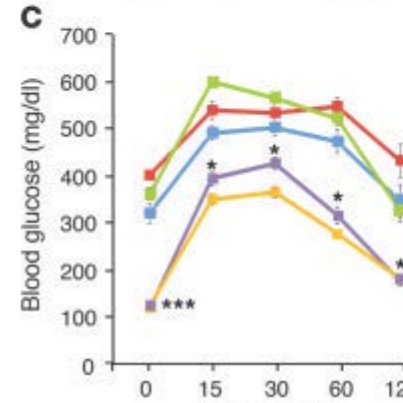
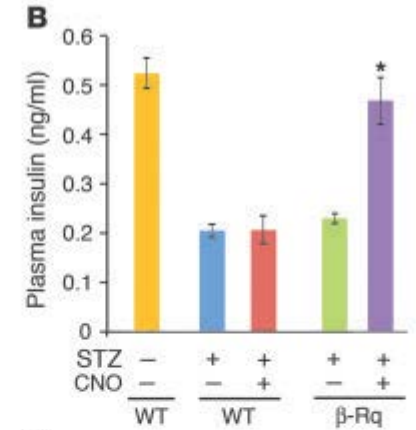
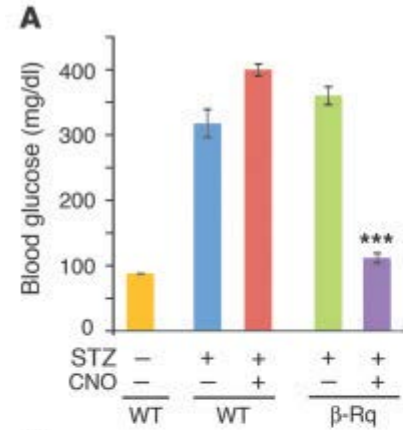
Similar results of optogenetics and chemogenetics



DREADDs work in non-neuronal cells



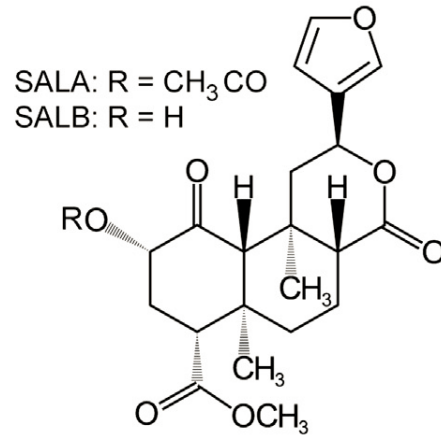
STZ: Streptozotocin



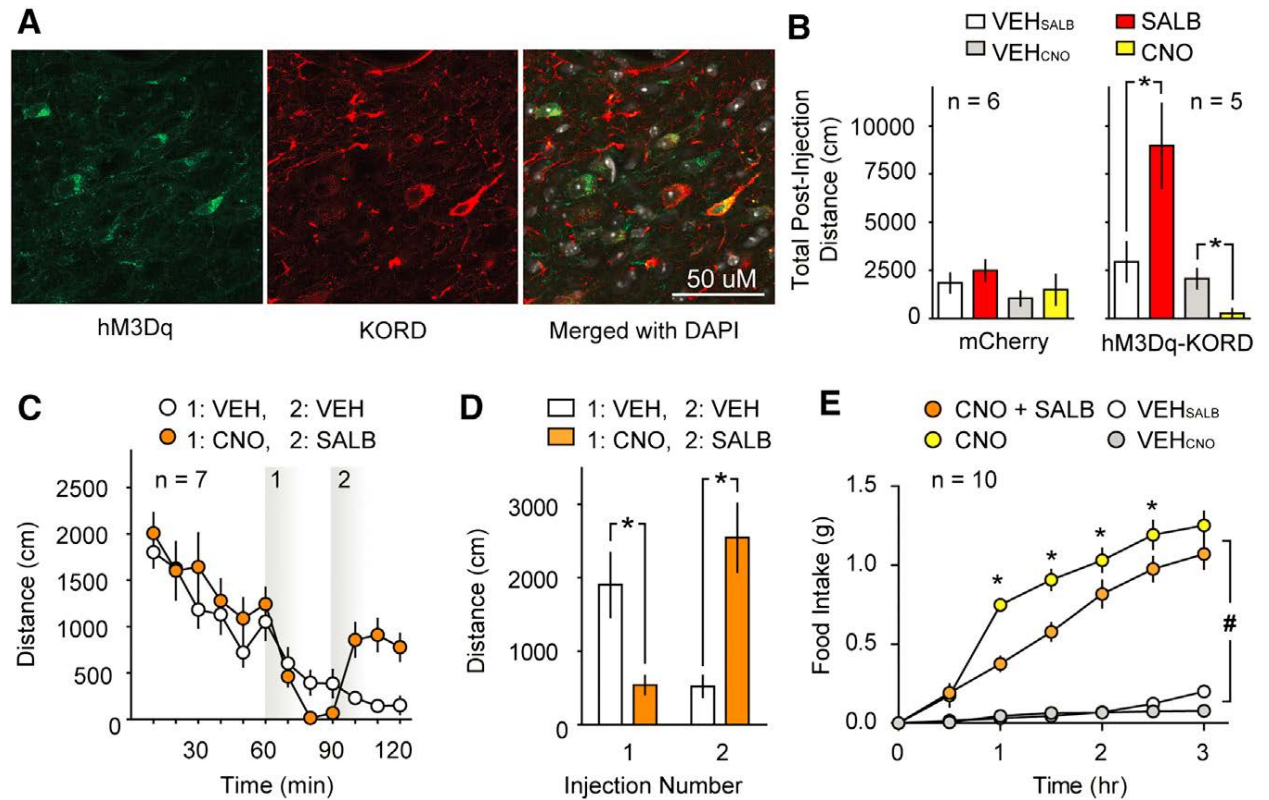
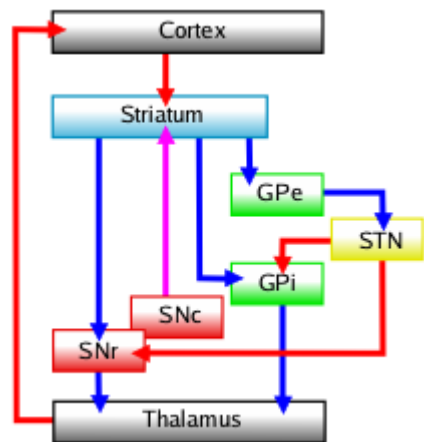
Shalini Jain and Jürgen Wess et al., 2013, J Clin Invest

Cendra Agulhon and Ken D. McCarthy et al., 2013, J Physiology

New DREADDs enables activating and inhibiting of cell activities in the same context

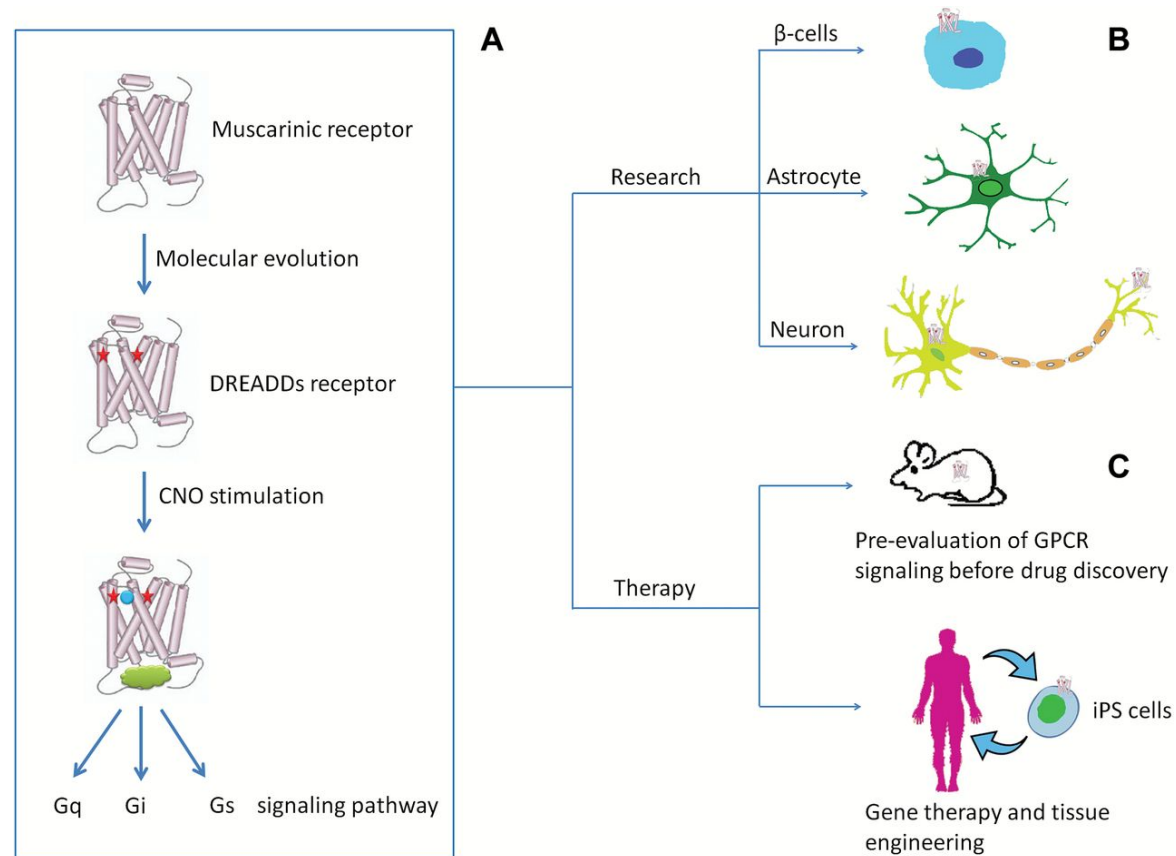


Gi-coupled DREADD using the kappa-opioid receptor as a template (KORD)



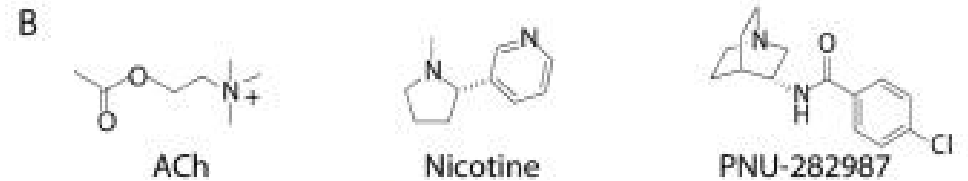
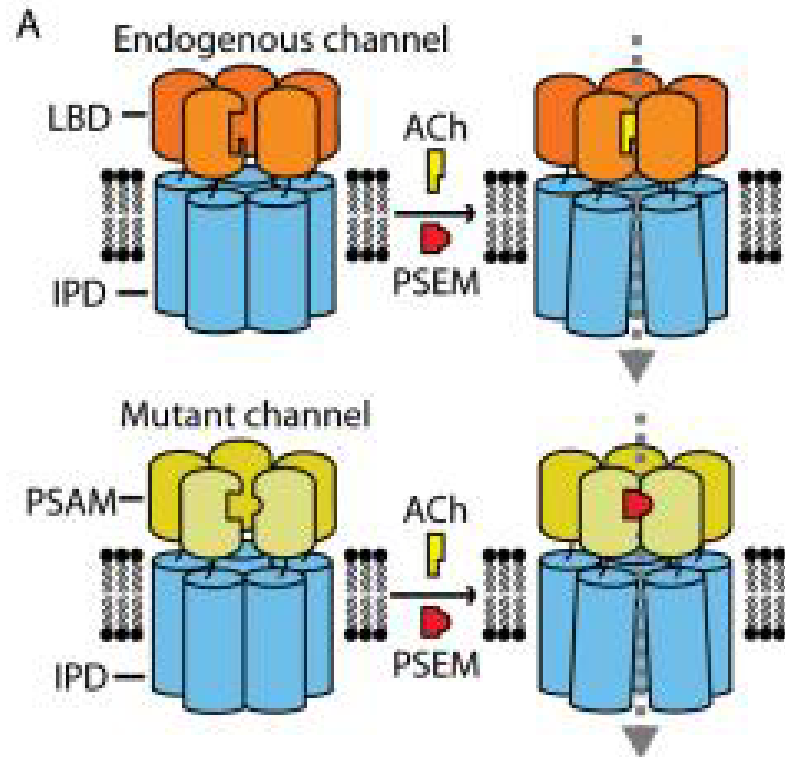
Eyal Vardy, J. Elliott Robinson, Chia Li, Michael J. Krashes and Bryan L. Roth et al., 2015, Neuron

Summary of DREADDs technology



Hu Zhu and Bryan Roth, 2014, International Journal of Neuropsychopharmacology

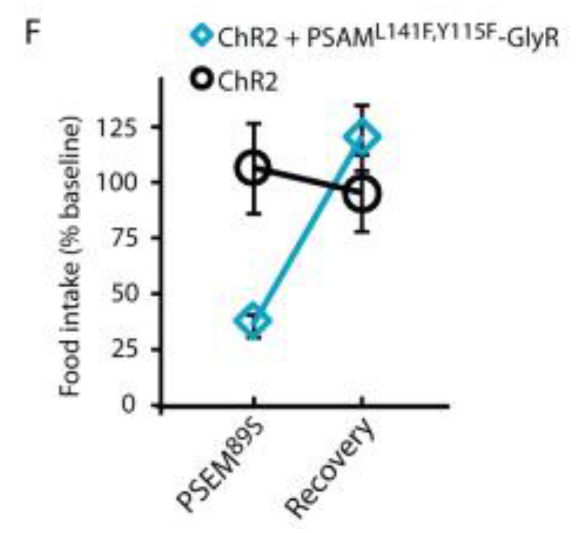
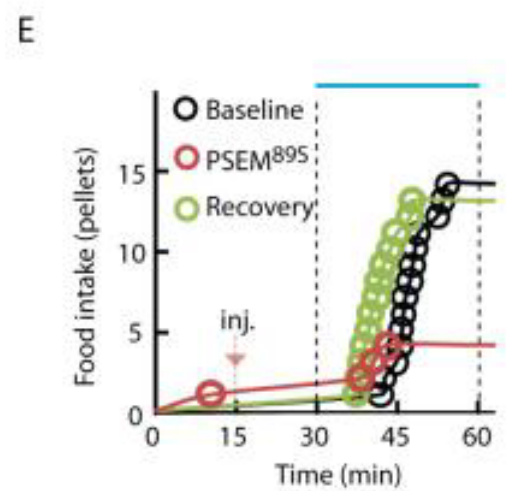
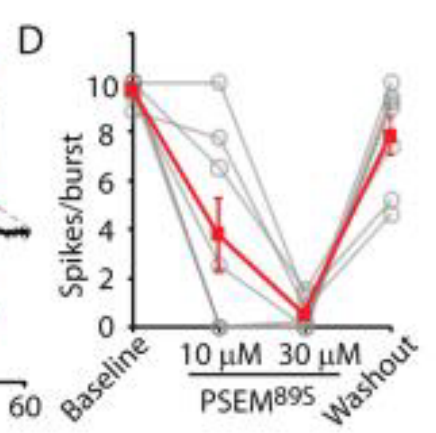
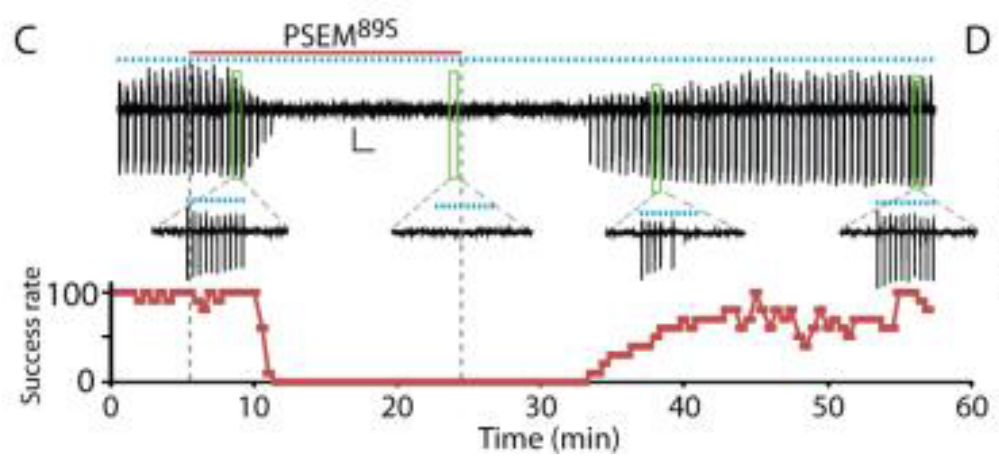
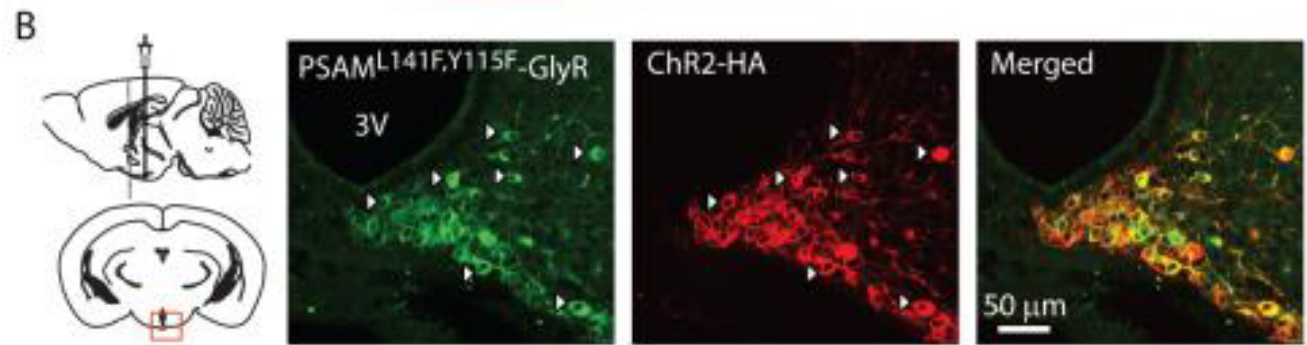
Chemogenetics using ion channels (PSAM and PSEM)



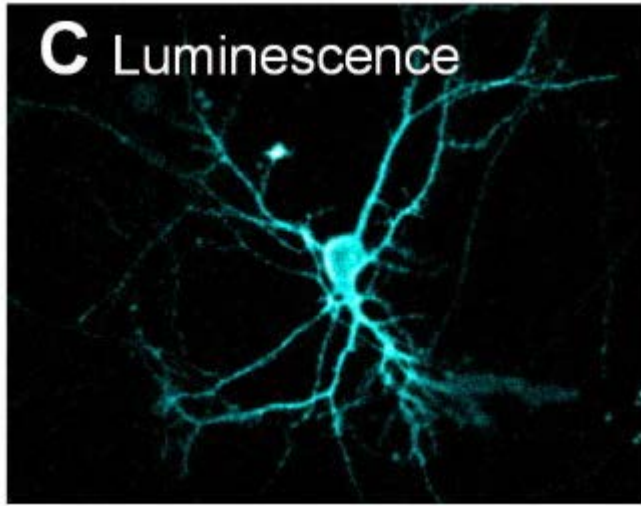
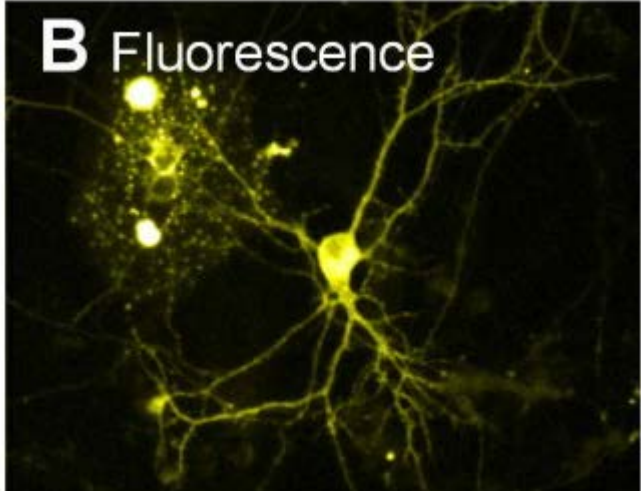
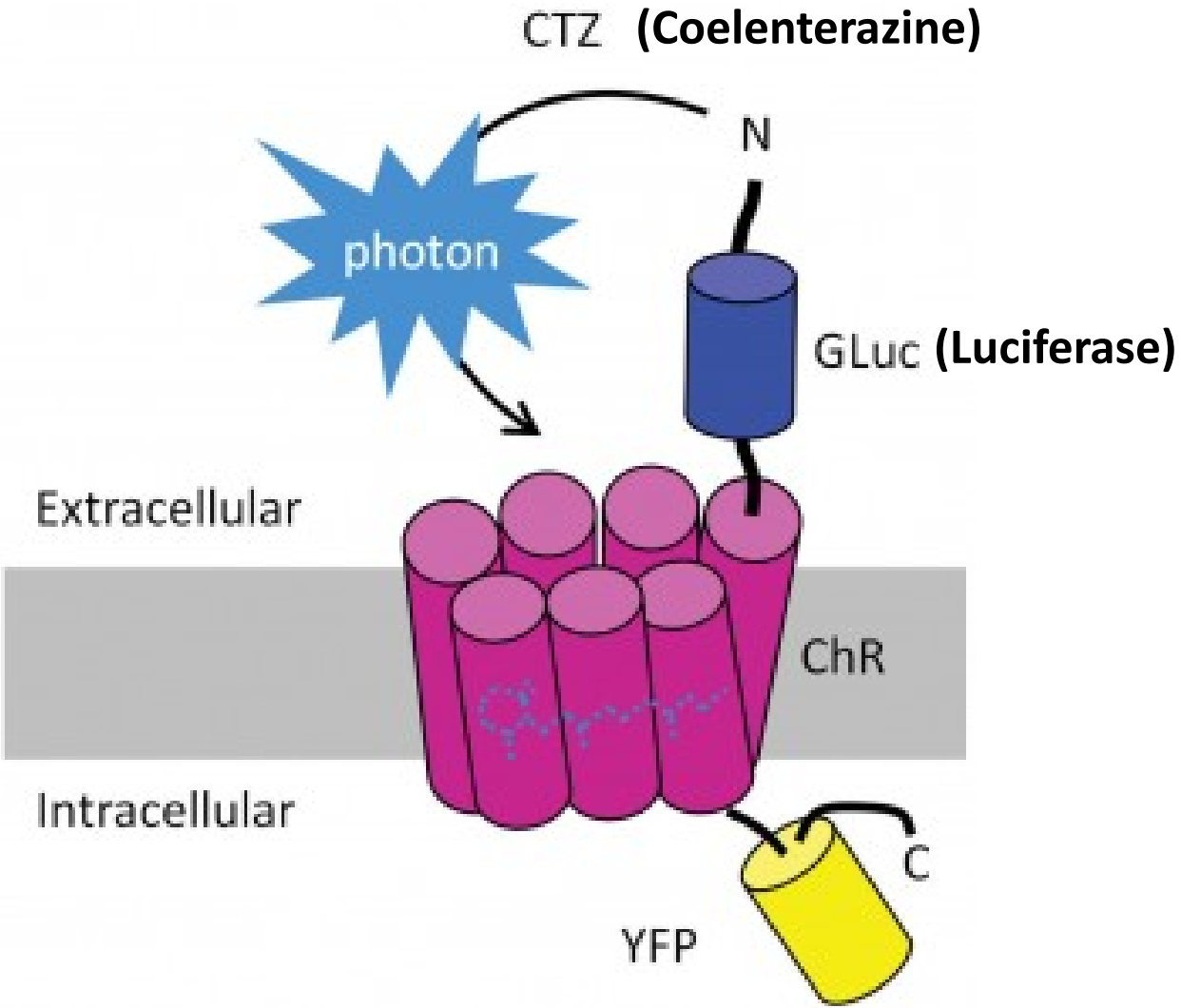
PSAM
(Pharmacologically Selective Actuator Module)

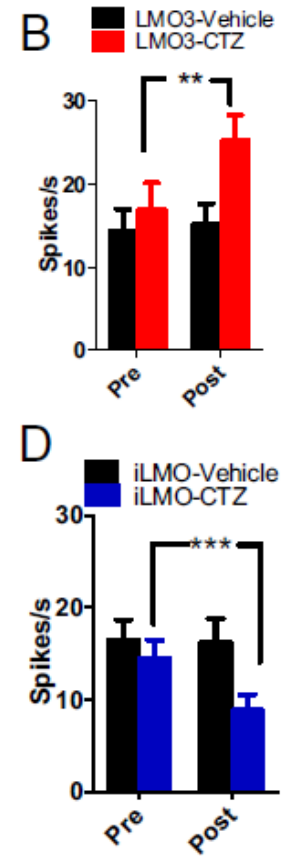
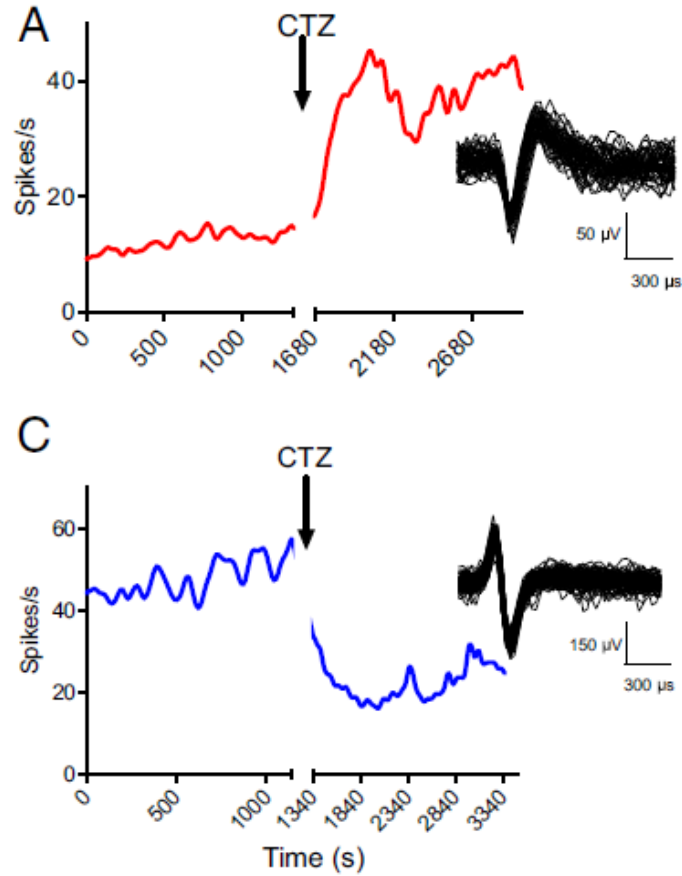
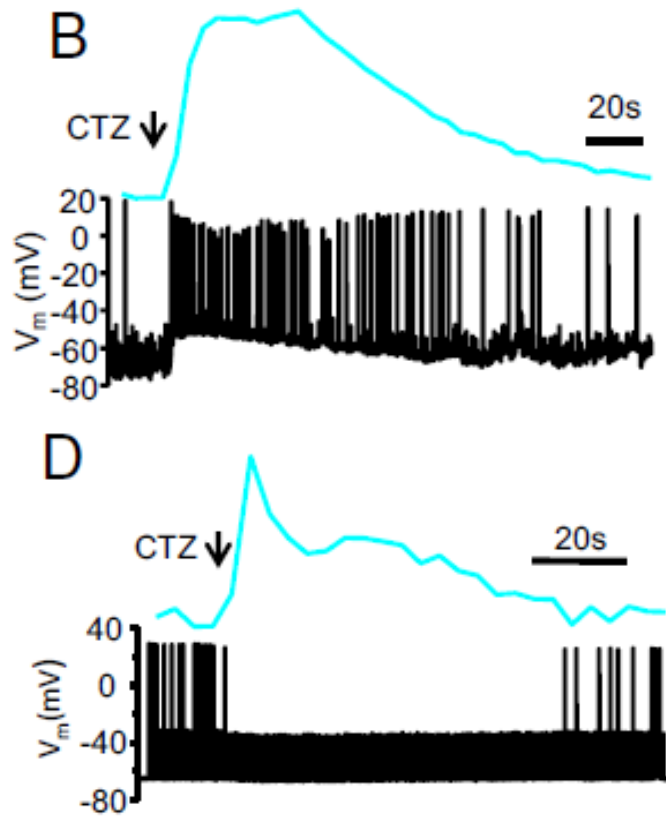
PSEM
(Pharmacologically Selective Effector Molecules)

Christopher J. Magnus, Peter H. Lee, Deniz Atasoy and
Scott M. Sternson et al., 2011, Science

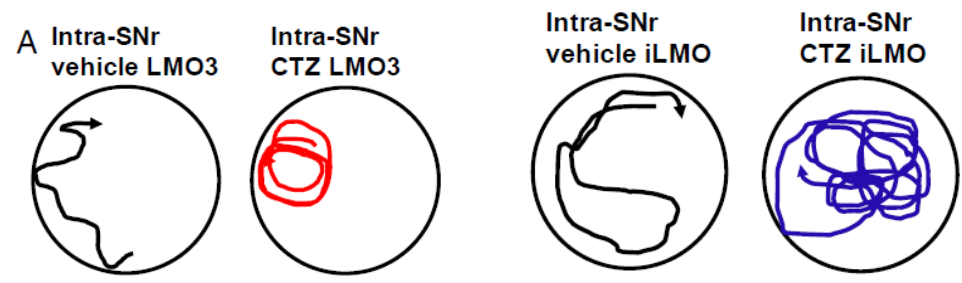
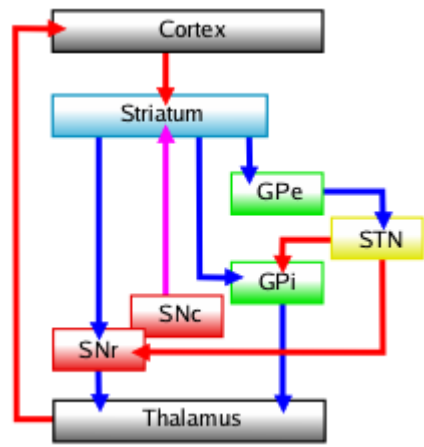


Luminopsins: converging optogenetics and chemogenetics

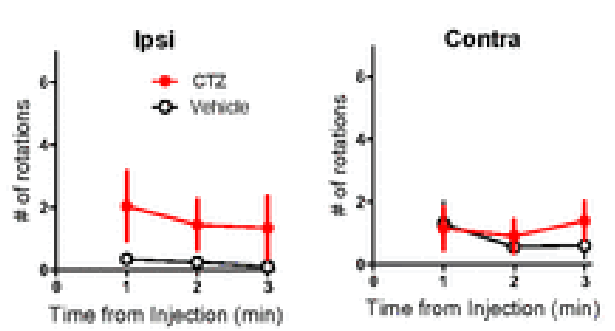




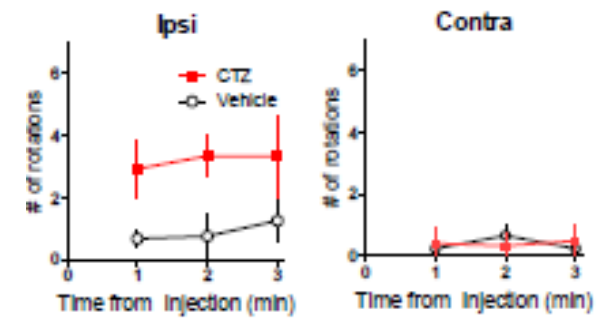
Ken Berglund and Ute Hochgeschwendera et al., 2015, PNAS



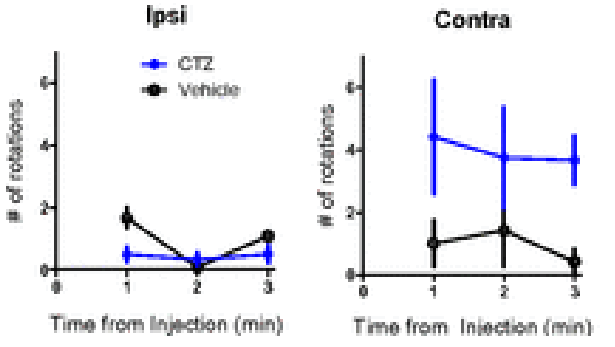
B Intra-SNr CTZ LMO3



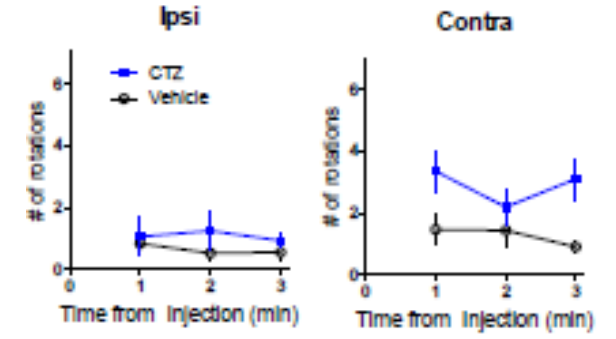
IV CTZ LMO3



C Intra-SNr CTZ iLMO



IV CTZ iLMO



Ken Berglund and Ute Hochgeschwendera et al., 2015, PNAS



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