

Concurrent and robust regulation of feeding behaviors and metabolism by orexin neurons

Jeong Ah Kim

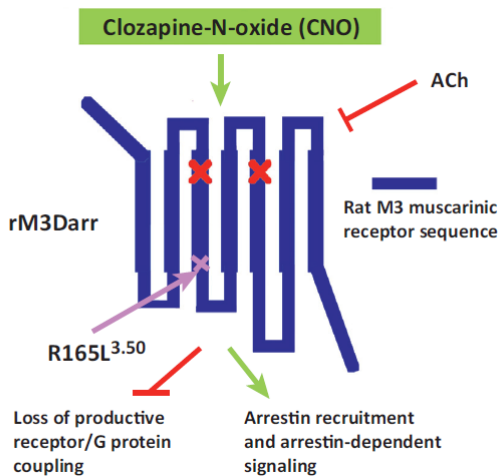
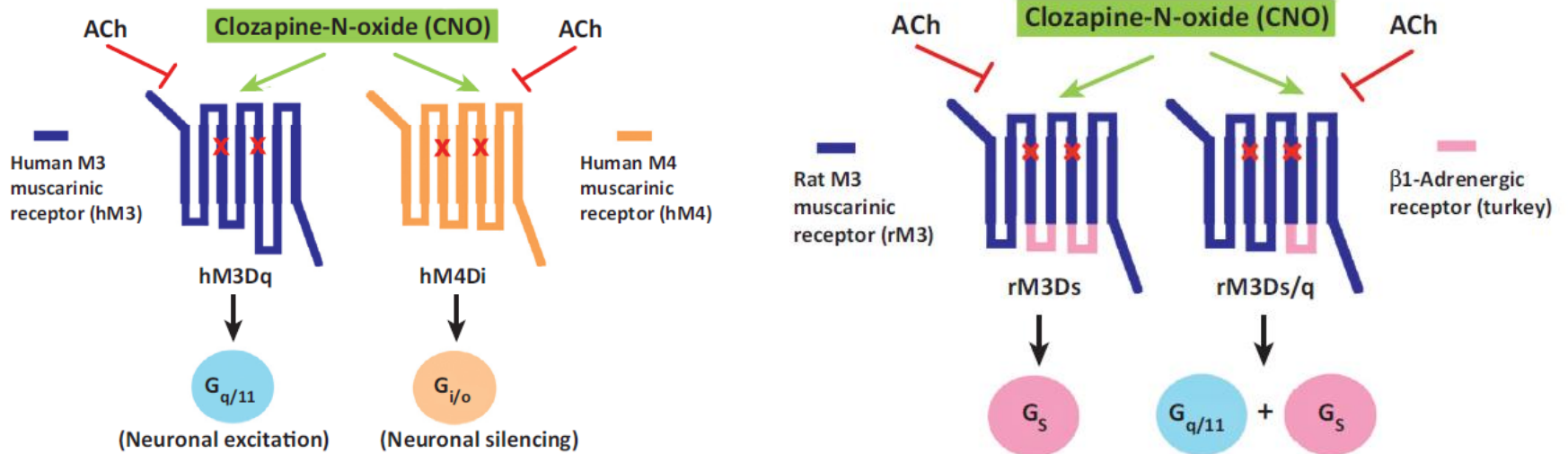
Brain & BioClock (BBC) Laboratory

Department of Brain and Cognitive sciences



Introduction

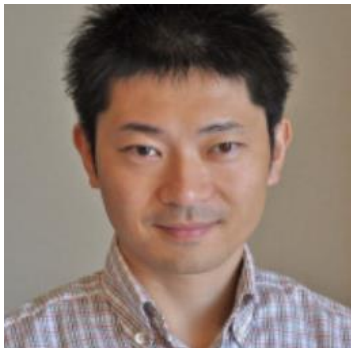
- DREADD: designer receptors exclusively activated by designer drugs



Author introduction

Concurrent and robust regulation of feeding behaviors and metabolism by orexin neurons

Ayumu Inutsuka ^a, Azusa Inui ^a, Sawako Tabuchi ^a, Tomomi Tsunematsu ^a,
Michael Lazarus ^b, Akihiro Yamanaka ^{a,*} Neuropharmacology (2014) 85:451-460



Akihiro Yamanaka

▪ Position

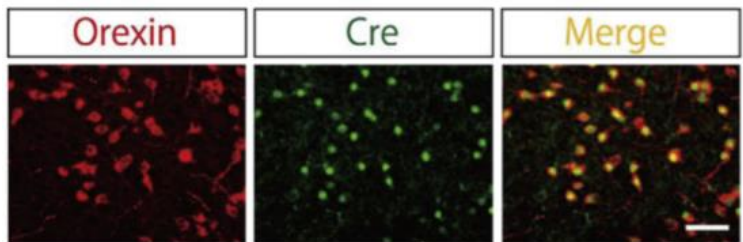
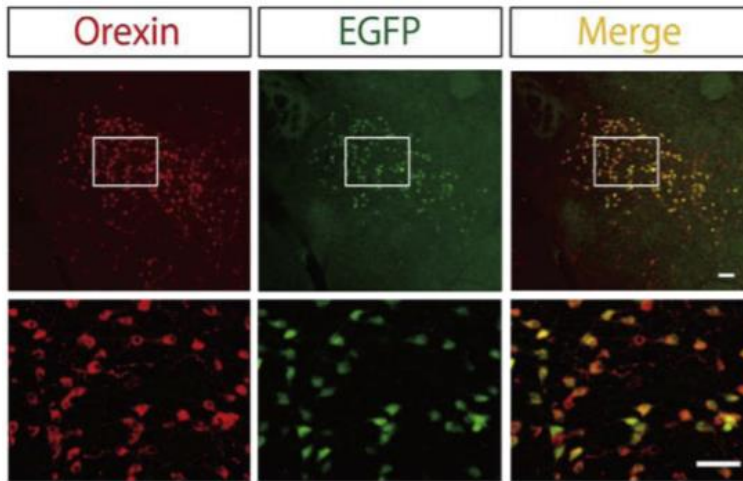
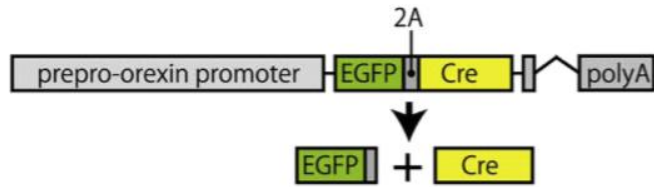
- Professor in Department of Neuroscience II, Research Institute of Environmental Medicine, Nagoya University

▪ Research area

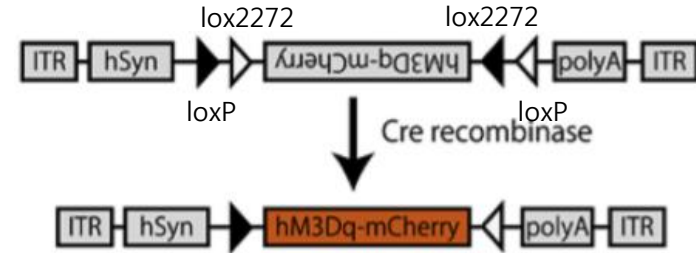
- 1) Mechanism of sleep/wakefulness regulation focusing on orexin/hypocretin producing neurons
- 2) Molecular Mechanisms of Nociception and Sensitization of Nociceptive Neurons
- 3) Neural Mechanisms of Pain/Nociception in Muscle and Fascia

Selectively activation of orexin neurons

Generation of orexin-Cre mice

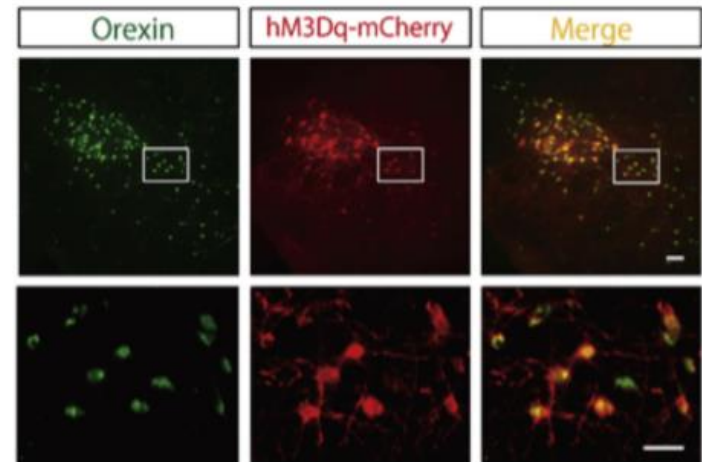


Schematic representation of the AAV vector expressing hM3Dq with a FLEX switch



- hM3Dq: Gq-coupled DREADD
- FLEX: flip-excision
- ITR, inverted terminal repeat
- hSyn: human synapsin promoter.

Immunohistochemistry in lateral hypothalamic area (LHA)

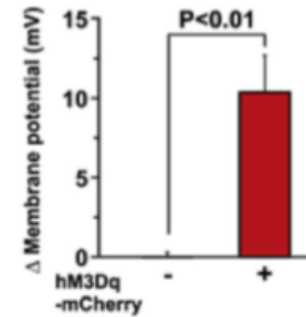


Pharmacogenetic activation of hM3Dq in orexin neurons

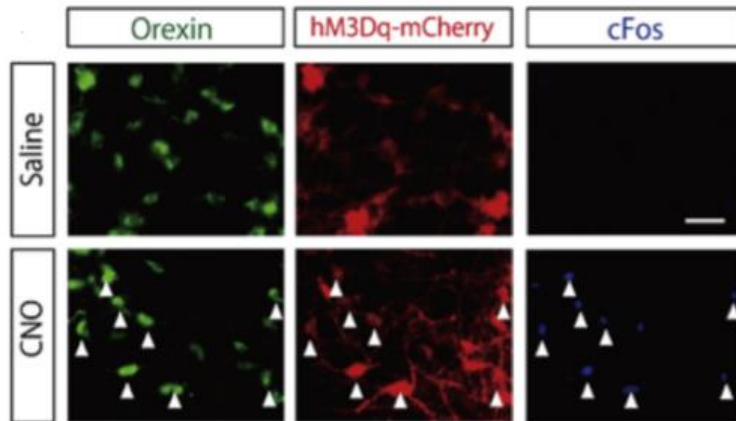
- Whole-cell, current clamp recording



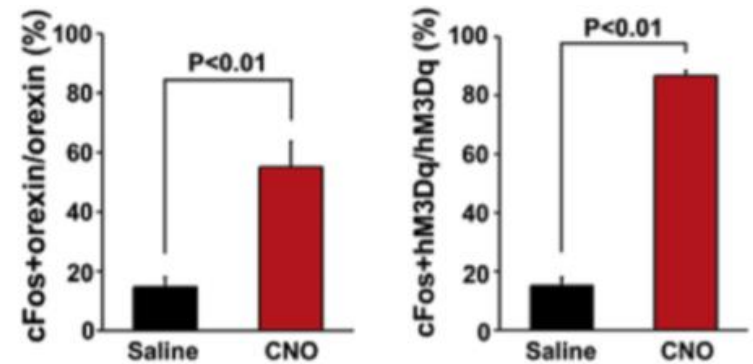
- Δ Membrane potential



- c-Fos immunoreactivity in orexin neurons



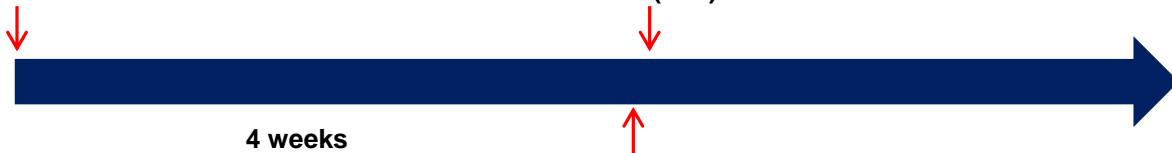
- Quantitative analysis of c-Fos activation of neurons



Feeding behaviors and metabolism

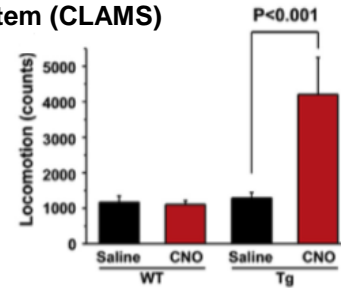
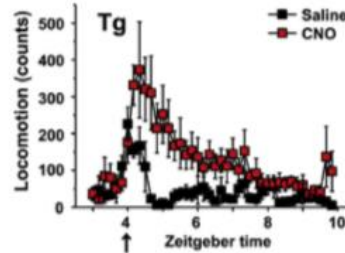
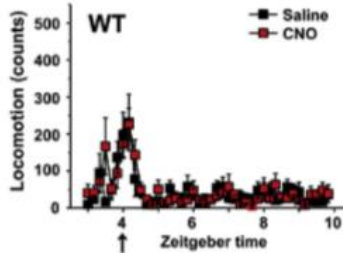
AAV vector injection

Injection with CNO (1.0 mg/kg, i.p.)
or saline at 12:00 (ZT4).

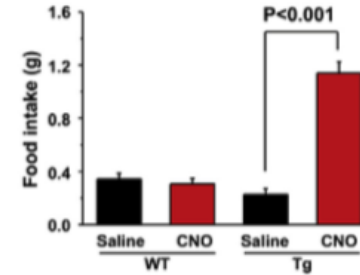
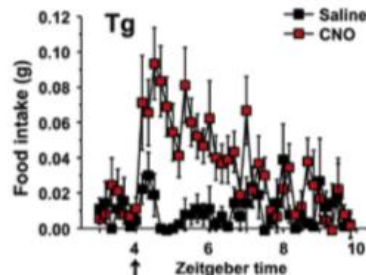
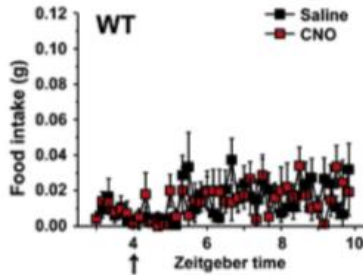


Monitored behavior using a
comprehensive laboratory animal
monitoring system (CLAMS)

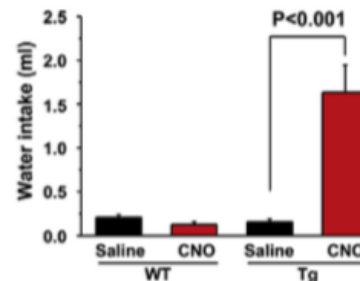
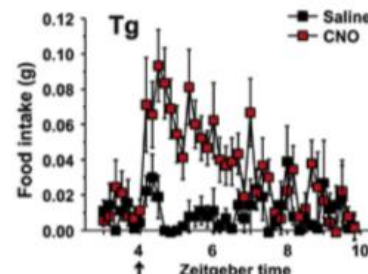
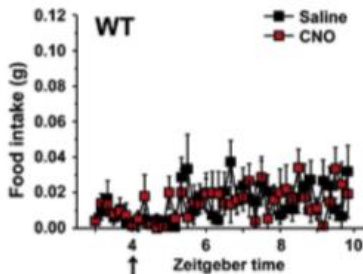
Ambulatory locomotion activity



Food intake

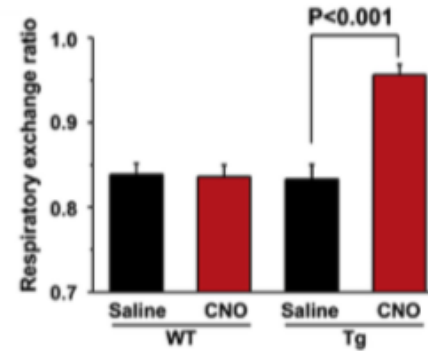
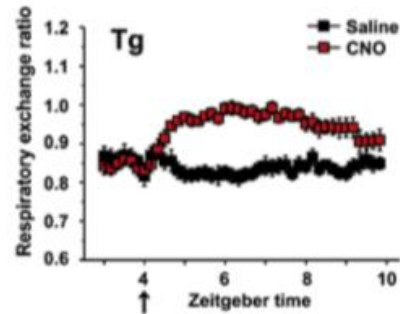
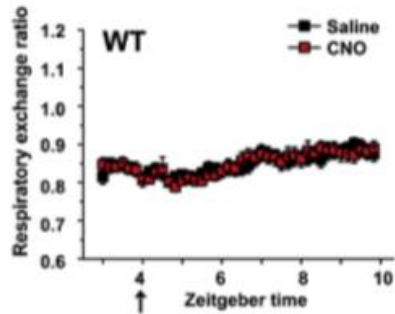


Water intake



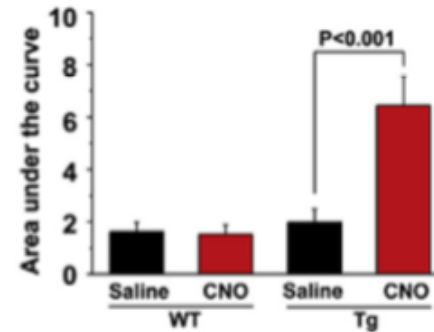
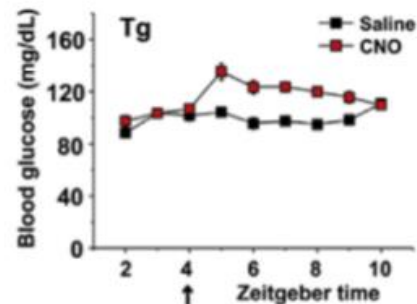
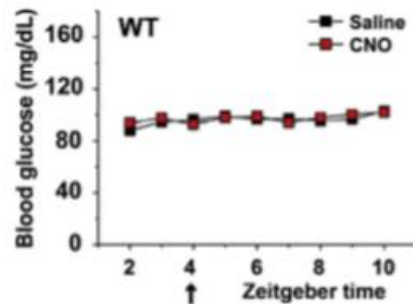
Feeding behaviors and metabolism

Respiratory exchange ratio



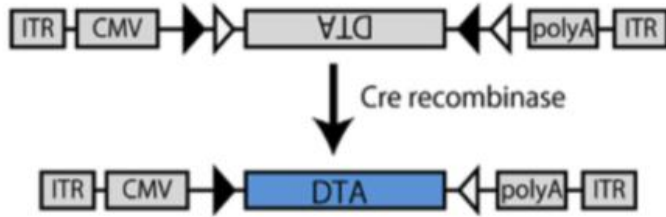
Blood glucose in fasting mice

⇒ All the mice were fasted from 20:00 (ZT12) on the day before the experiments

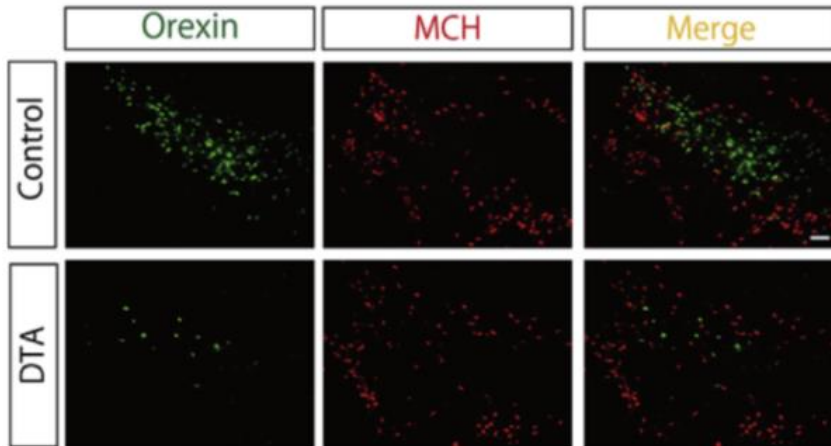


Selective ablation of orexin neurons by DTA

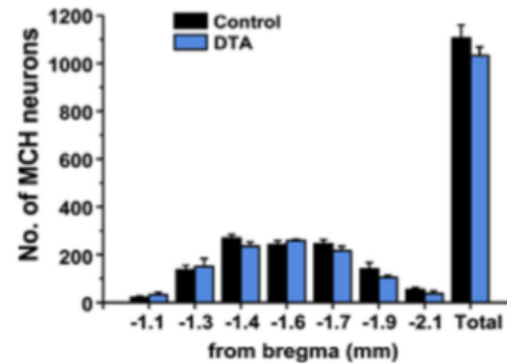
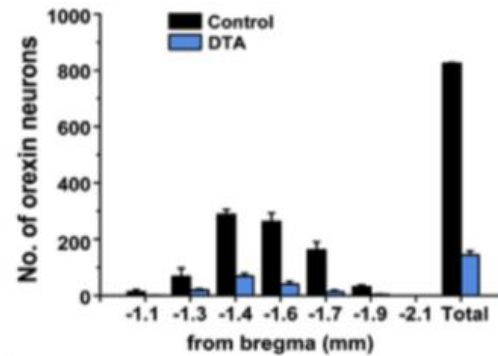
- Cre-dependent AAV vector expressing DTA



- Immunohistochemistry in lateral hypothalamic area

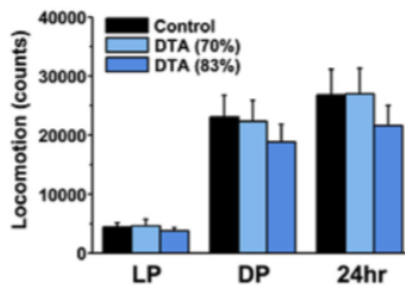
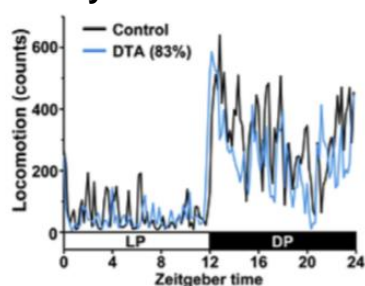
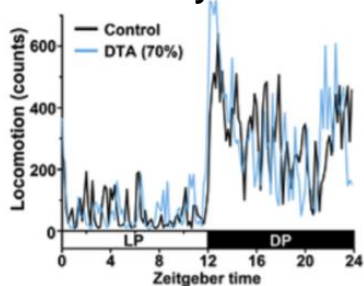


- MCH: Melanin-concentrating hormone

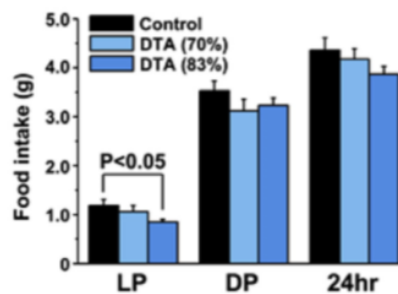
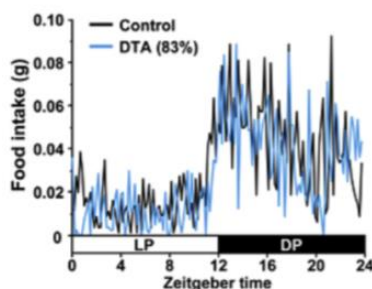
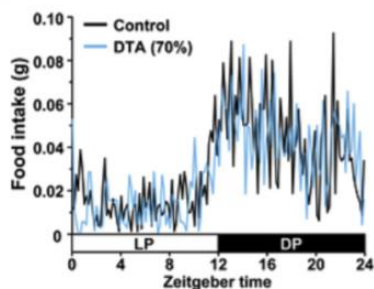


Feeding behaviors and metabolism

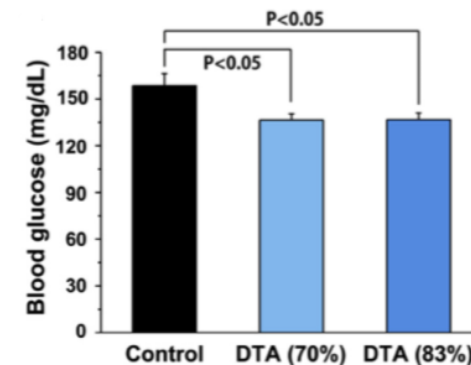
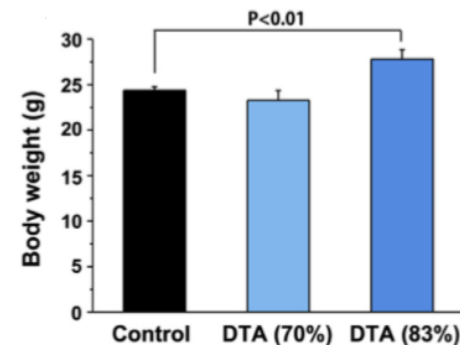
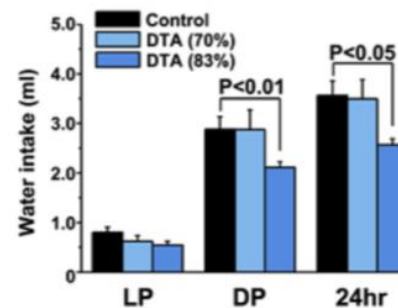
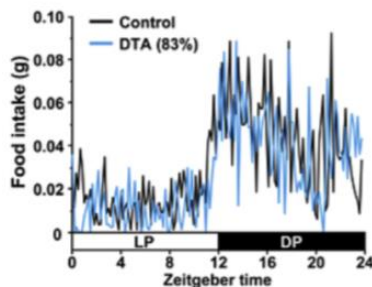
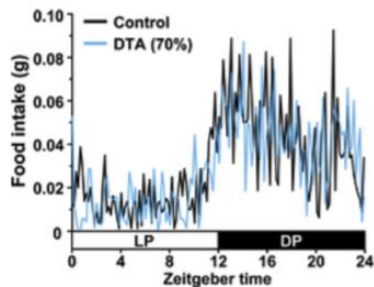
■ Ambulatory locomotion activity



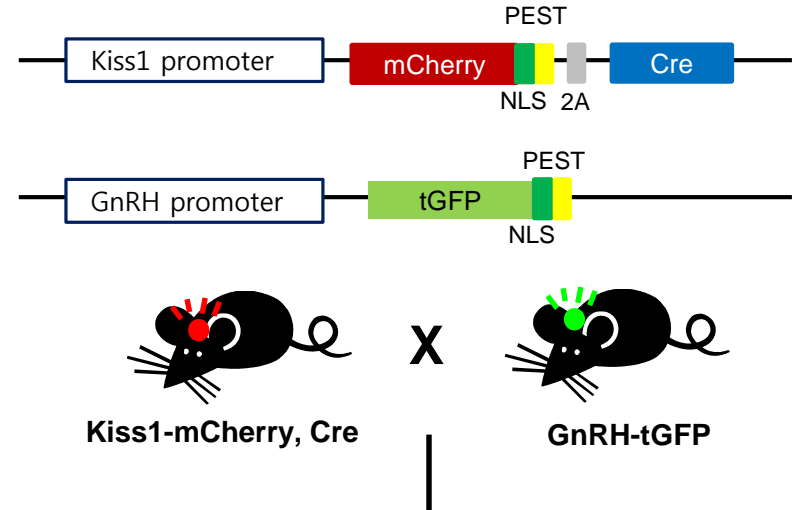
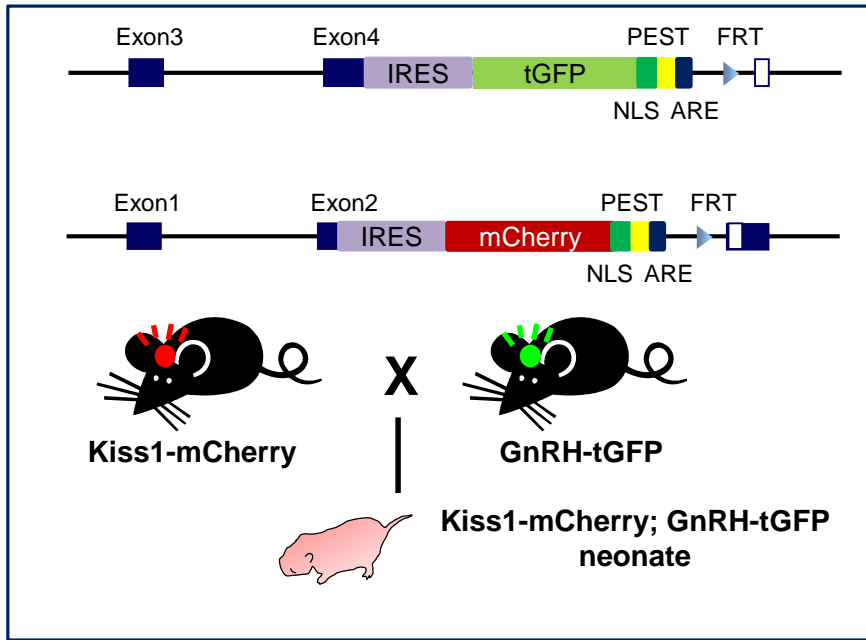
■ Food intake



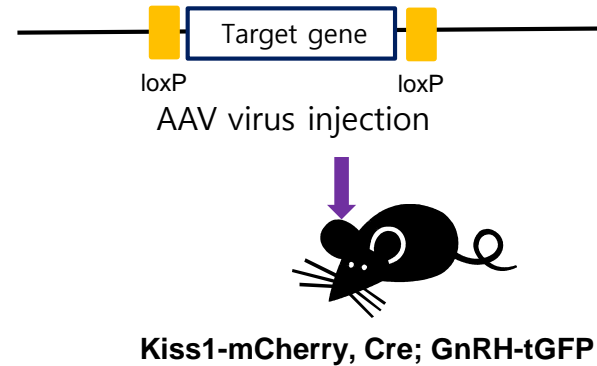
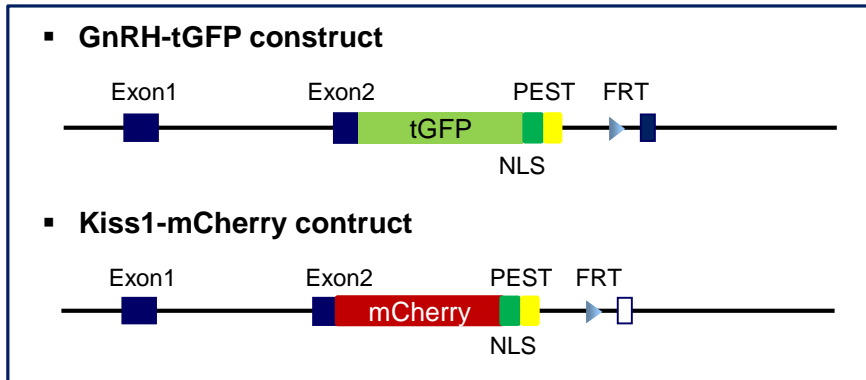
■ Water intake



Discussion



- Kiss1 activator: TTF1, CUX1-p200 EAP1
- Kiss1 repressor: EAP1, YY1, and CUX1-p110



References

1. Inutsuka A, Inui A, Tabuchi S, Tsunematsu T, Lazarus M, Yamanaka A. (2014) Concurrent and robust regulation of feeding behaviors and metabolism by orexin neurons. *Neuropharmacology*. 85:451-60
2. Wess J, Nakajima K, Jain S. (2013) Novel designer receptors to probe GPCR signaling and physiology. *Trends Pharmacol Sci*. 34(7):385-92