

The endocannabinoid system controls food intake via olfactory processes



FOOD INTAKE

Neuronal plasticity

Learning

Inflammation

Sleep

Locomotion

3000 a.C.

Giovanni Marsicano

"EndoCannabinoids and NeuroAdaptation"

INSERM U862 NeuroCentre Magendie,

Bordeaux, France

5^{eme} Colloque Annuel
ITMO-PMN



HPA axis

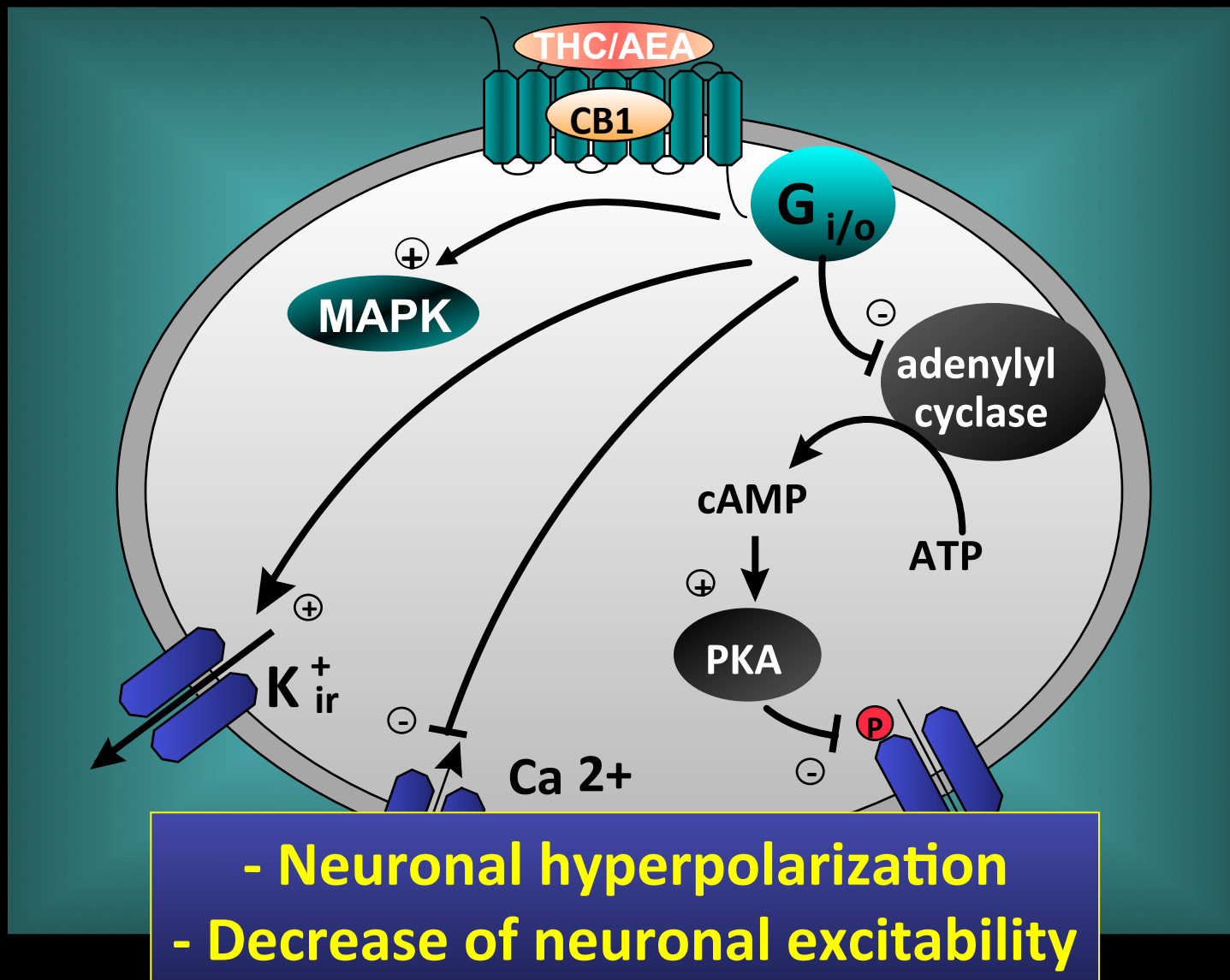
Pain perception

Rewarding

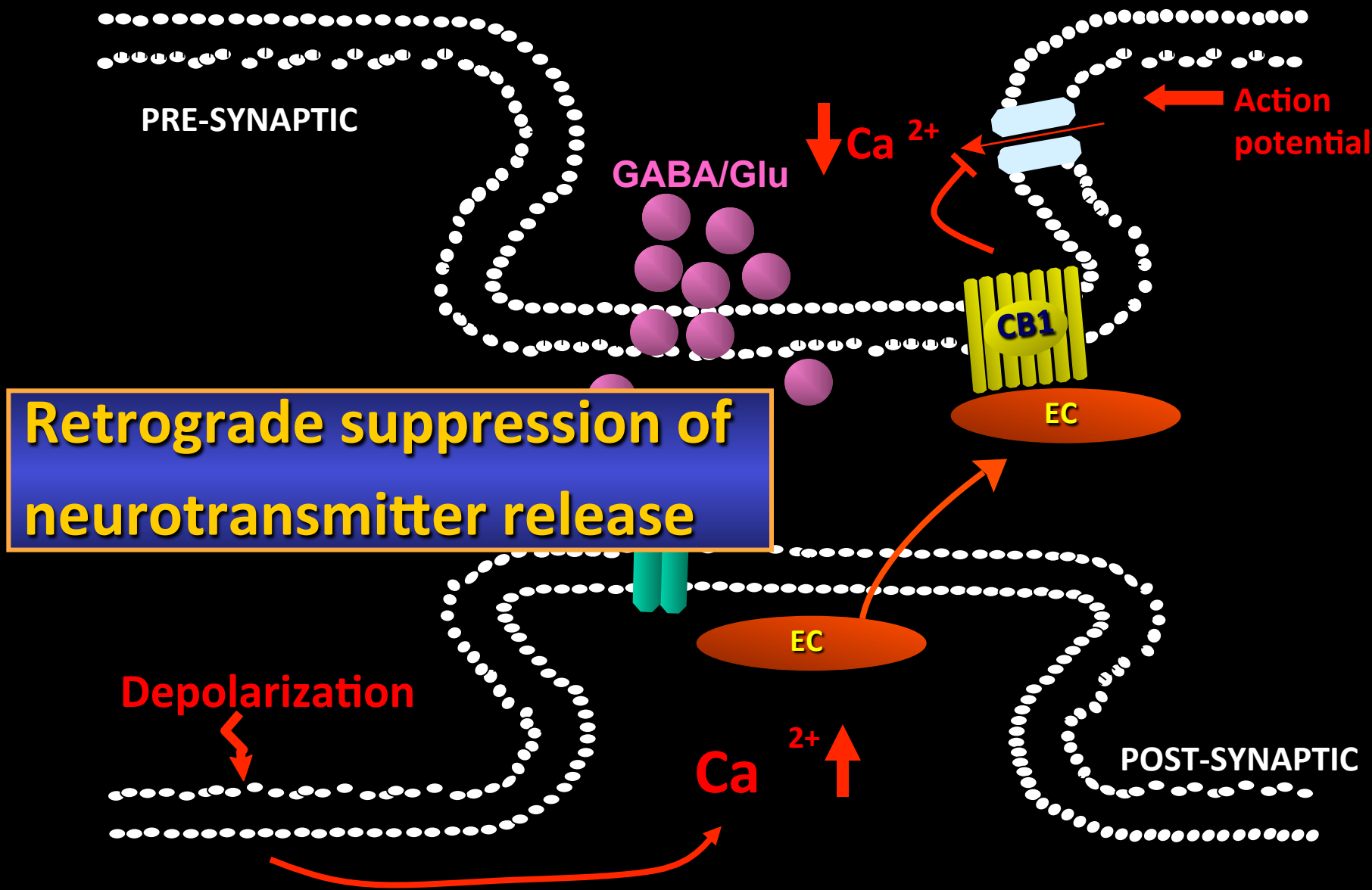
Neurogenesis

Sexual Behaviour

Mechanisms of action of CB1



Retrograde control of synaptic transmission



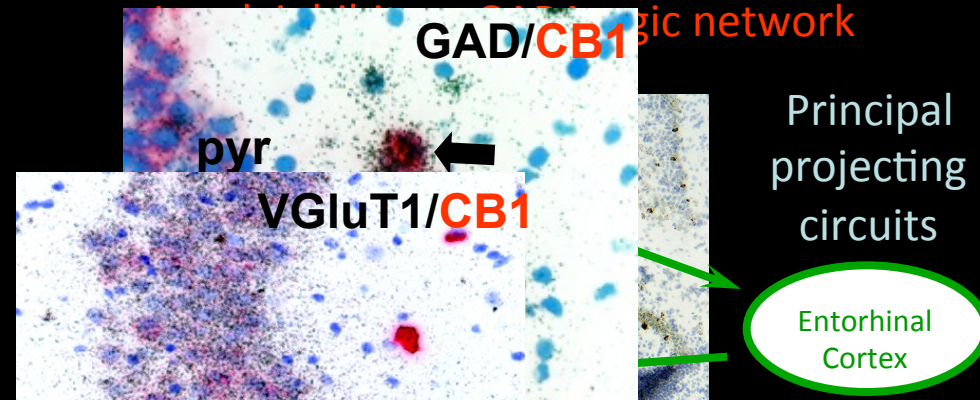
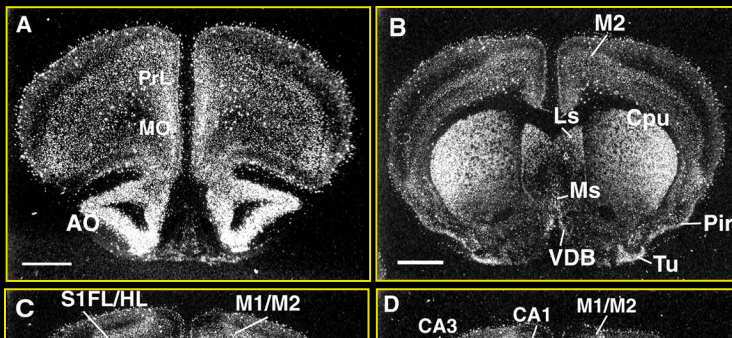
**To eat or not to eat,
that is the question!**



Where is CB1 expressed?

Many different
brain regions

Distinct neuronal
subpopulations



Are there cell-type specific functions of CB1?

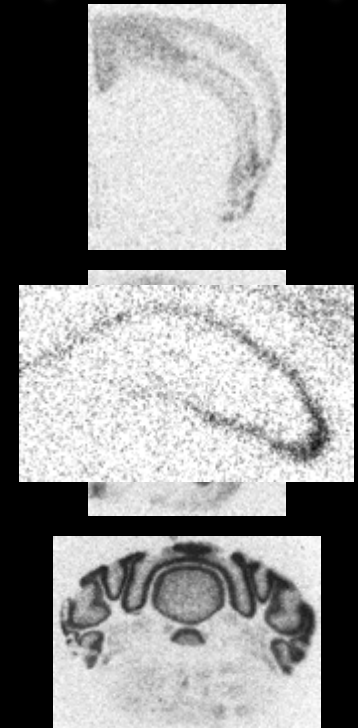
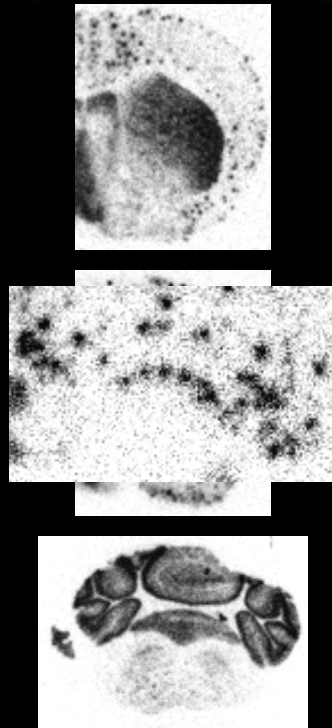
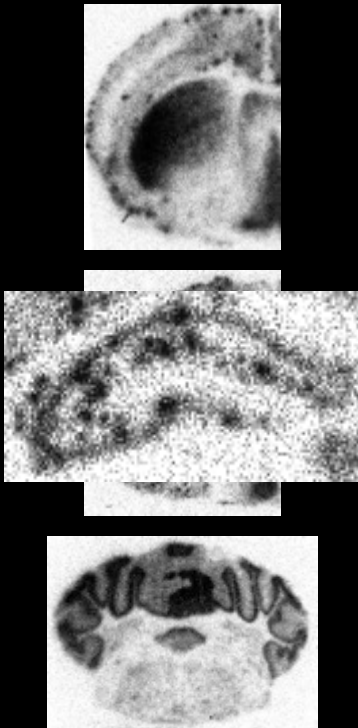
Deletion of CB1 from specific neuronal populations

- Cre/LoxP system
- CB1 “floxed” mice crossed with NEX-Cre or Dlx 5/6-Cre mice
- ISH analysis of CB1 mRNA expression

WT

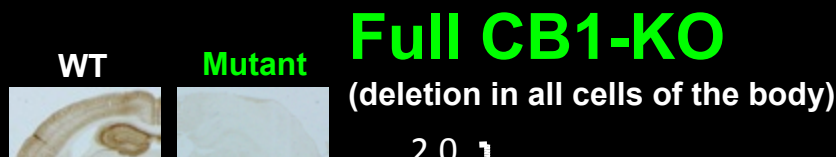
**Cortical Glutamatergic Neurons
(Glu-CB1-KO)**

**GABAergic
Neurons
(GABA-CB1-KO)**



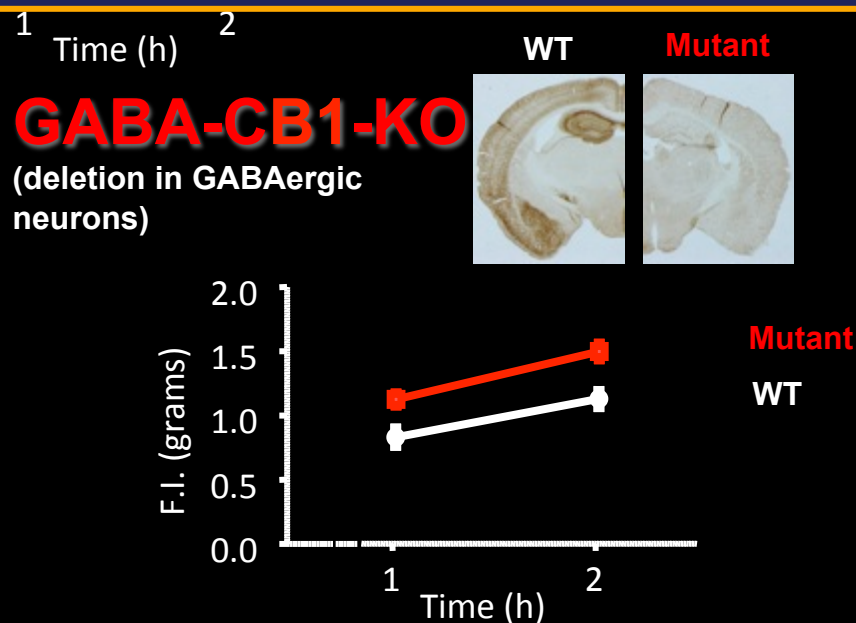
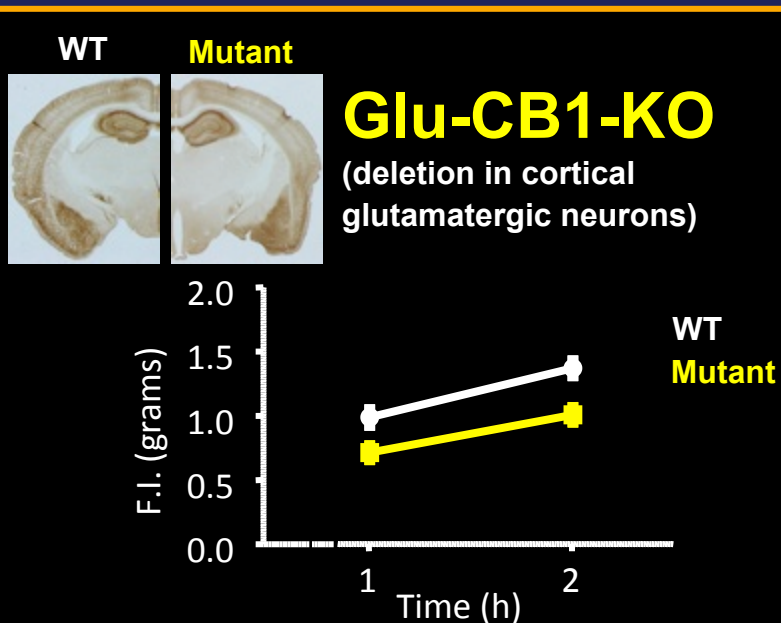
Cell specific roles of CB1 in fasting-induced food intake

Fasted CB1-KO eat less than controls (Di Marzo et al., Nature 2001)

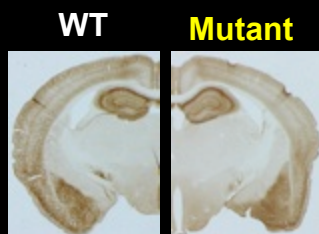


Bimodal control of food intake by the endocannabinoid system

Bellochio et al., *Nat Neurosci.* 2010

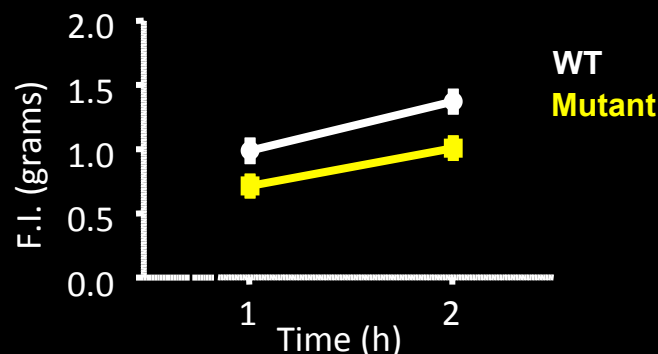


Focus on glutamatergic transmission



Glu-CB1-KO

(deletion in cortical glutamatergic neurons)



GLU



FOOD INTAKE

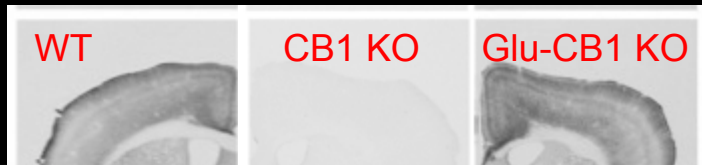
CB1 receptors on cortical glutamatergic neurons **mediate** fasting-induced food intake

Where does this happen?

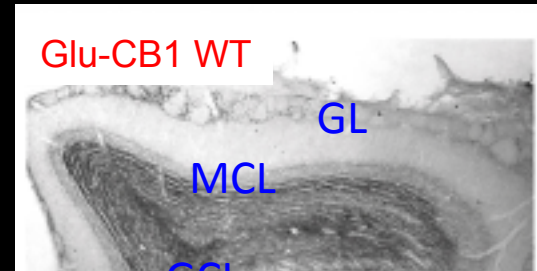
ANATOMY

CB1 expression in the brain

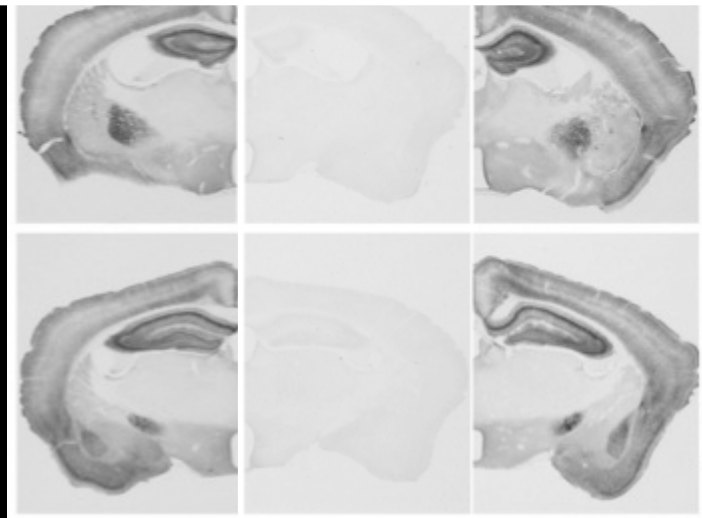
Pedro Grandes
Bilbao



The Olfactory Bulb (OB)



Glu-CB1 KO presents a **decrease** in CB1 expression on GCL of the OB

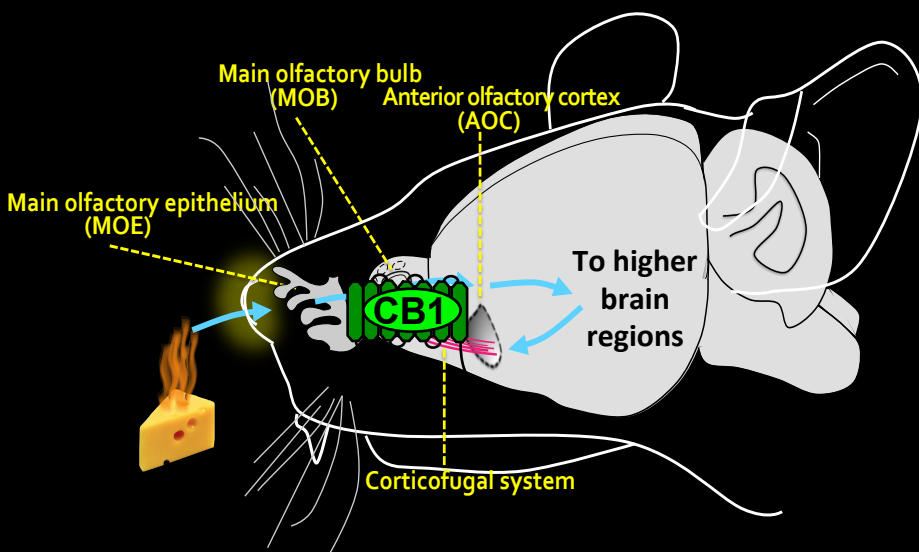


GL: Glomeruli
MCL: Mitral cell layer
GCL: Granular cell layer

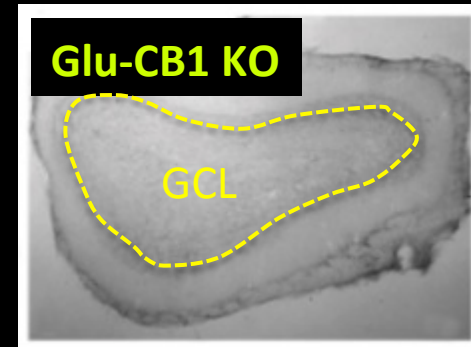
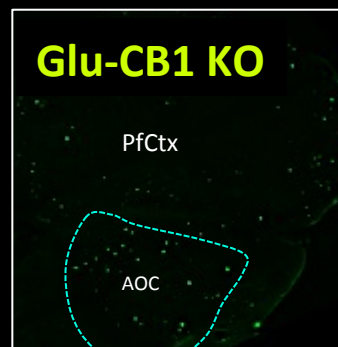
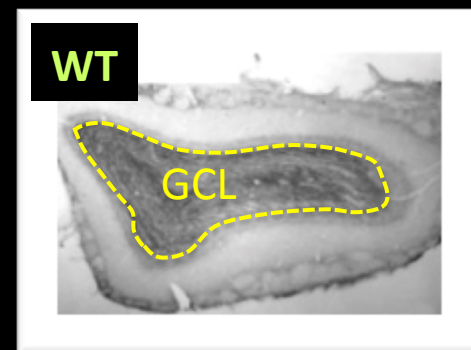
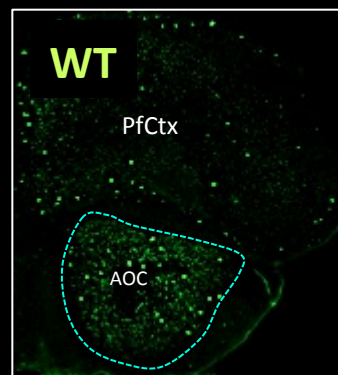
Olfactory Circuits

CB1 mRNA
AOC

CB1 protein
MOB



**CB1 receptors are at
glutamatergic terminals of
terminals of corticofugal fibers**

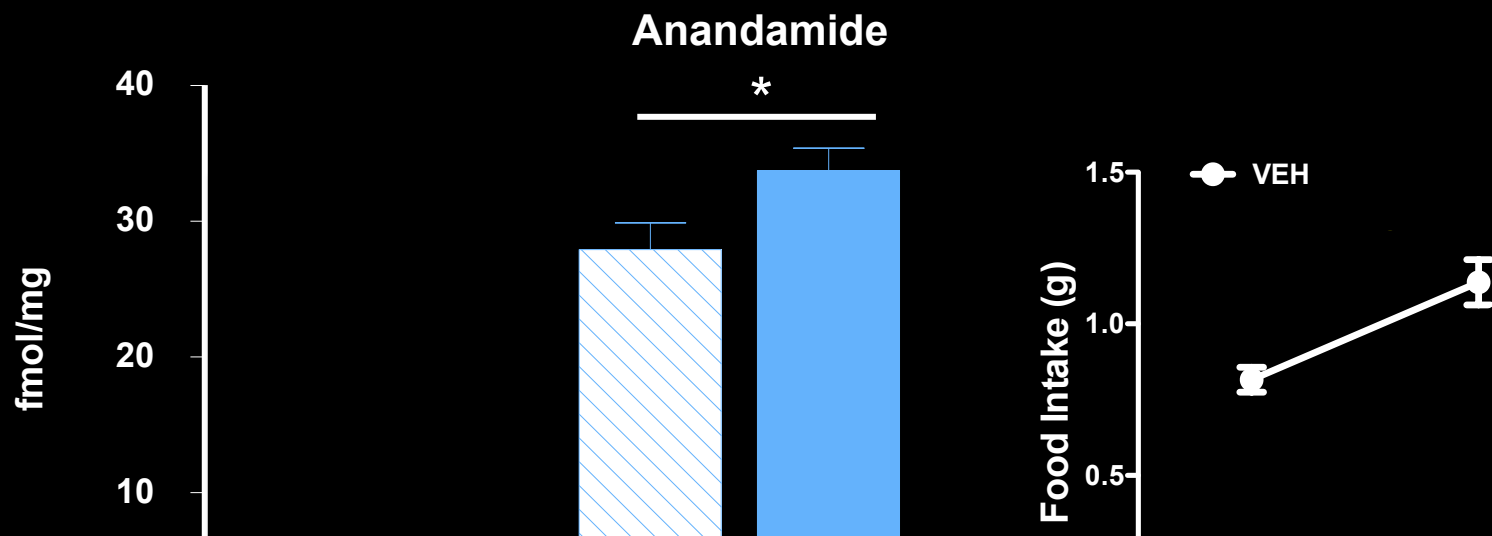


**Does CB1 regulate food intake *via* modulation of
glutamatergic CORTICOFUGAL transmission to the MOB?**

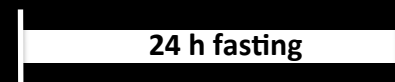
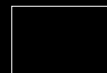
OB endocannabinoids & Food Intake



AM251: CB1 Antagonist



**CB1 receptors in the OB mediate
fasting-induced hyperphagia**

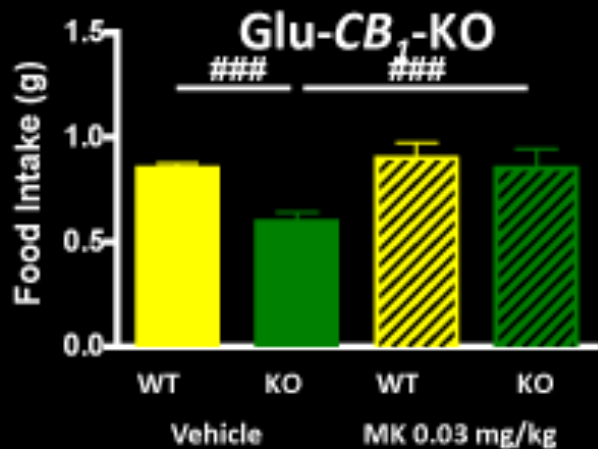


OB endocannabinoids & Food Intake



Systemic

Glu-blockade reverts the hypophagic phenotype of the Glu-CB1 KO

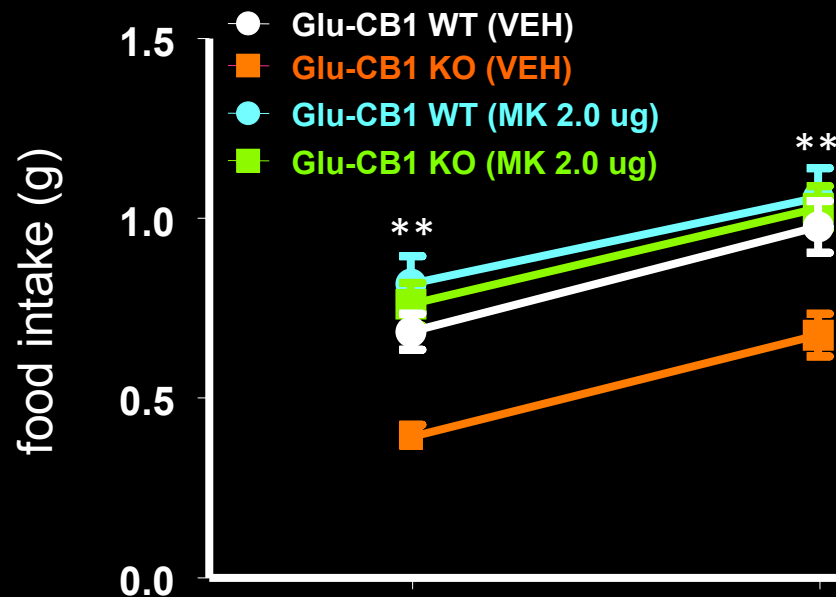


MK: MK801 (NMDA antagonist)



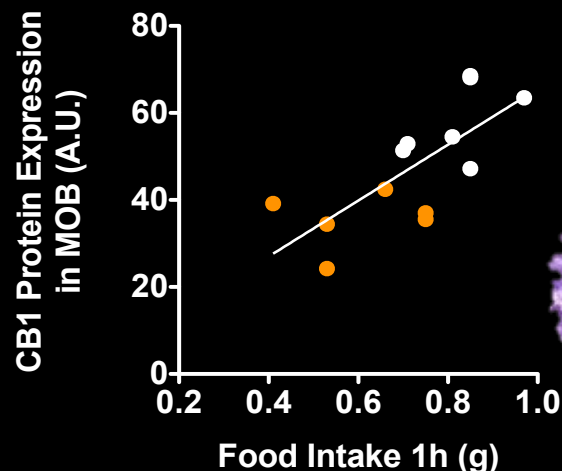
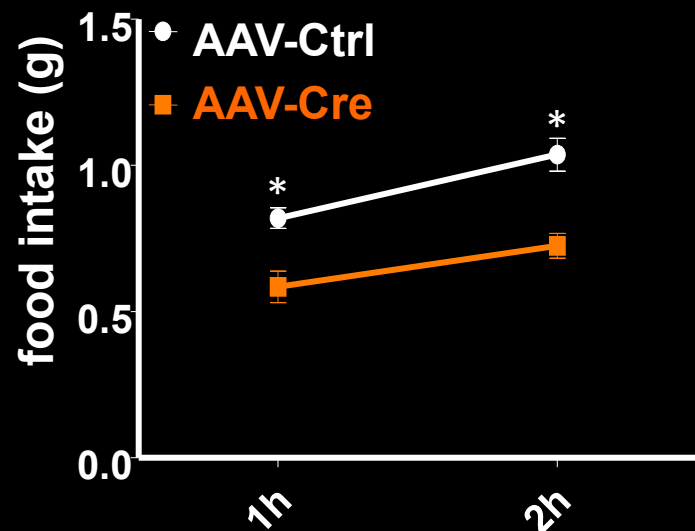
Olfactory bulb

Glu-blockade into the OB reverts the hypophagic phenotype of the Glu-CB1 KO



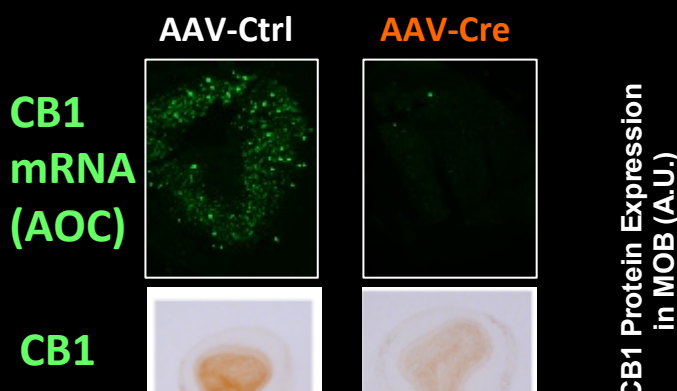
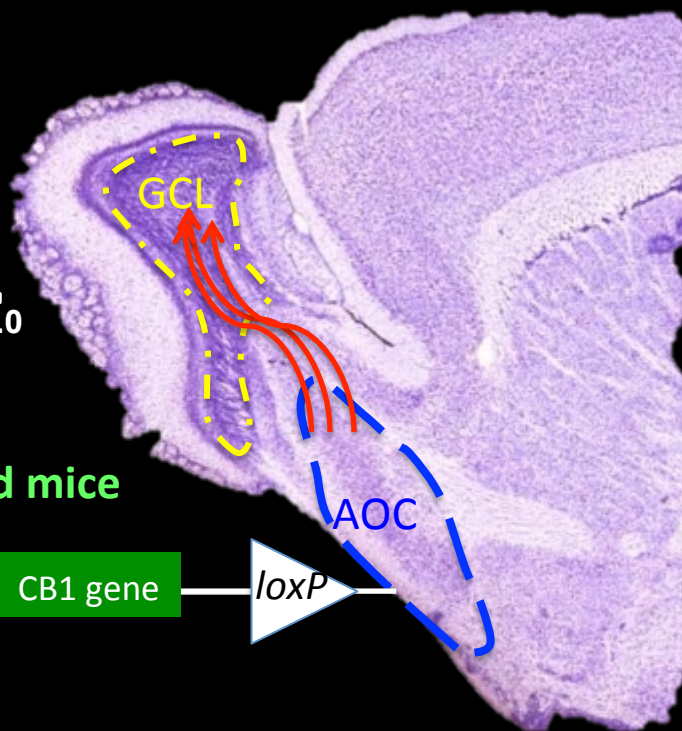
CB1 receptors control food intake *via* regulation of glutamatergic transmission in the OB

Are really corticofugal fibers involved?

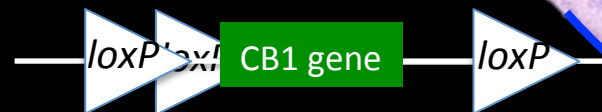


AAV-Ctrl

AAV-Cre



CB1 floxed mice



AOC: Anterior Olfactory Cortex

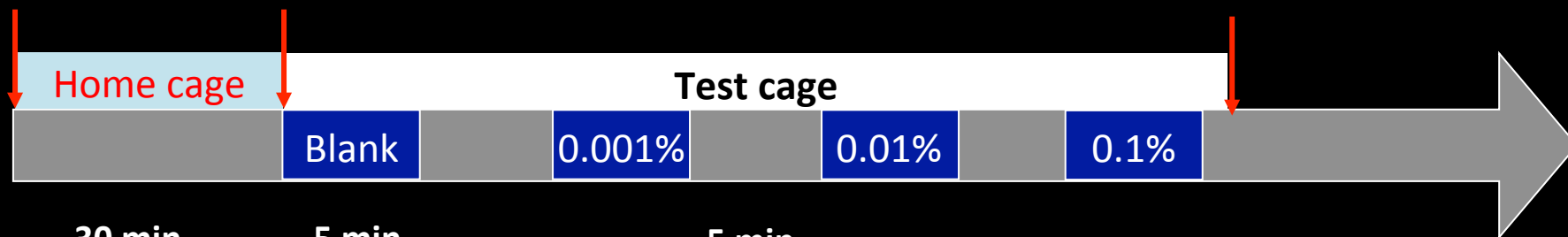
GCL: Granular Cell Layer

CB1 receptors on corticofugal projections to the OB mediate fasting-induced food intake

What about OLFACTION?

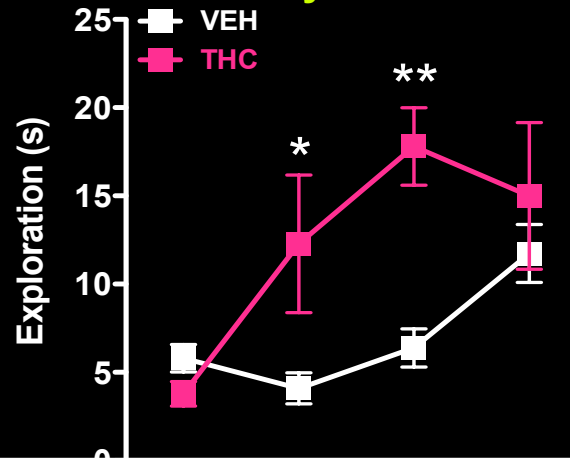
Olfactory Detection (Threshold)

VEH OR THC

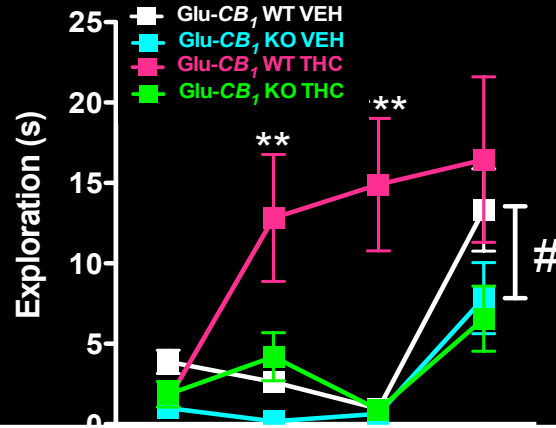


What about OLFACTION?

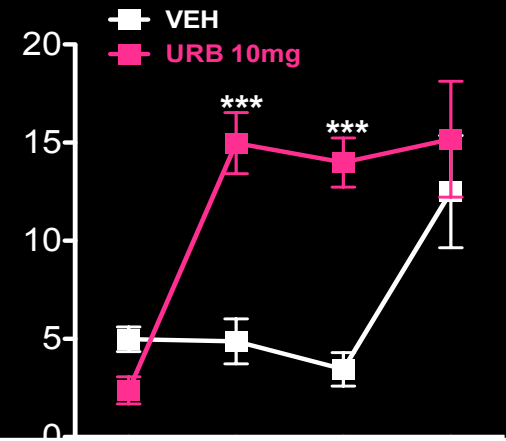
Does THC impact olfactory threshold ?



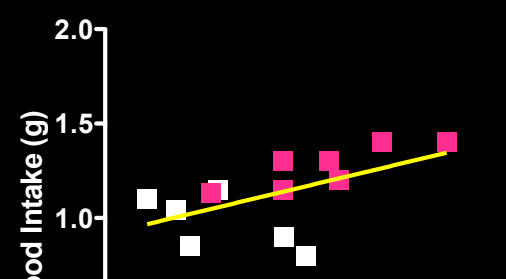
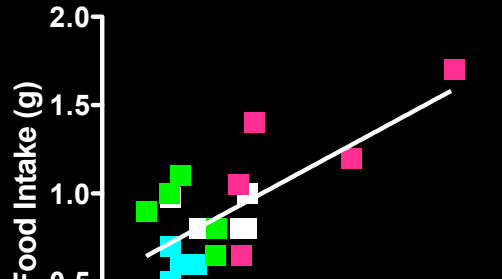
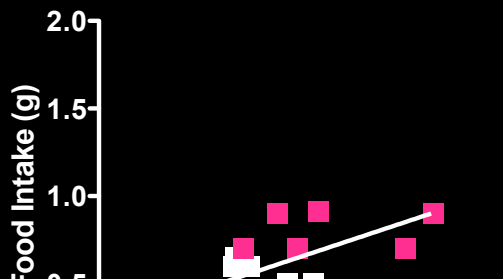
Does this depend on Glu transmission?



Are endocannabinoids involved?

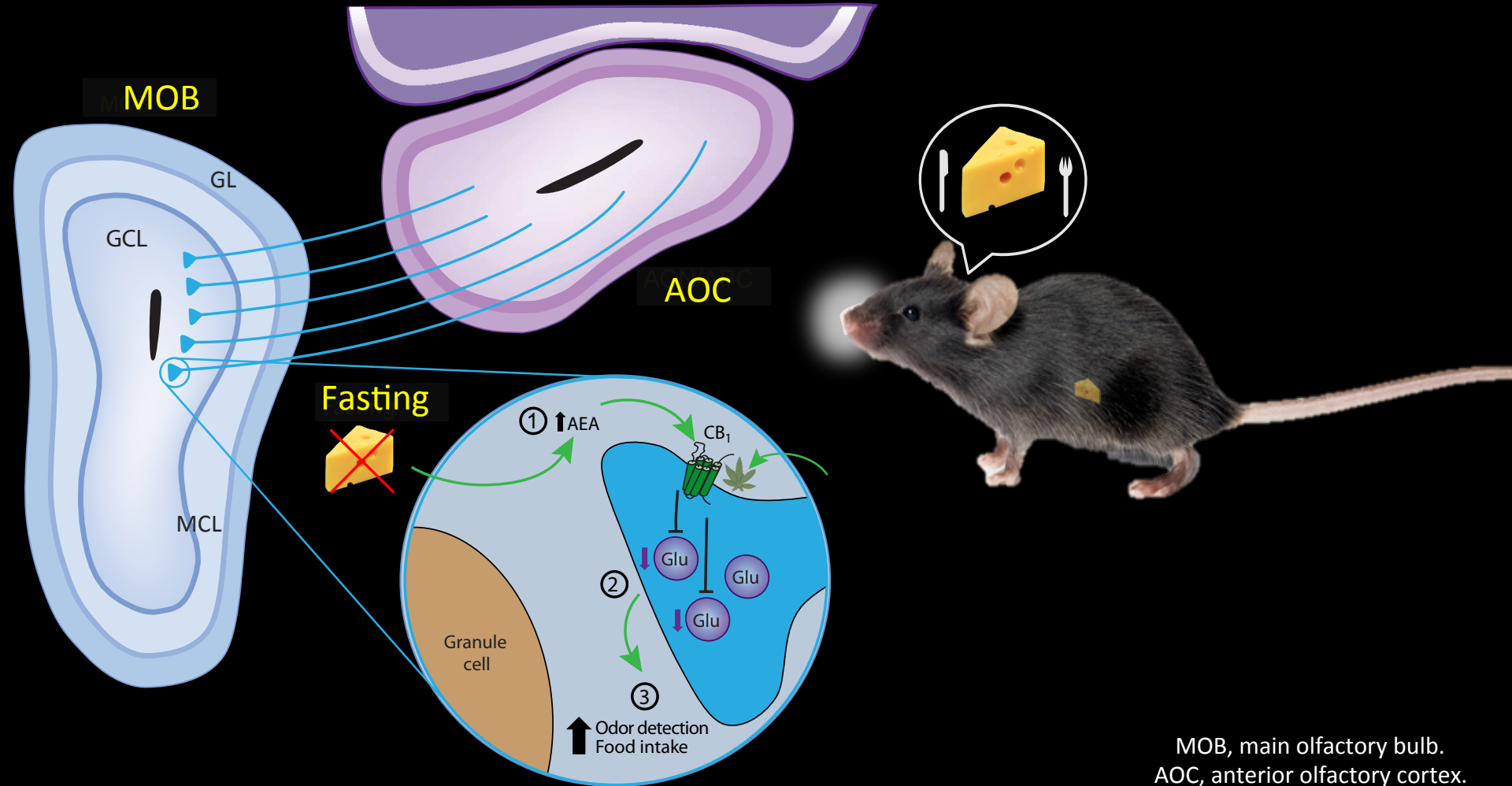


Link to food intake?



CB1 activity modulates olfaction and food intake *via* the same mechanisms

CONCLUSION



MOB, main olfactory bulb.
AOC, anterior olfactory cortex.
GL, glomerular layer.
GCL, granular cell layer.
MCL, mitral cell layer.