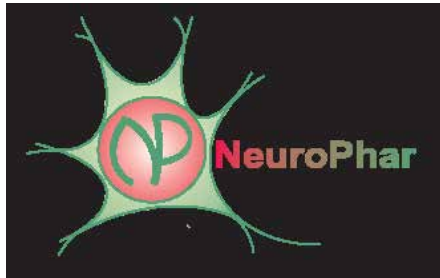




Universitat
Pompeu Fabra
Barcelona

Implicación de las Orexinas/Hipocretinas en las propiedades adictivas de las drogas de abuso

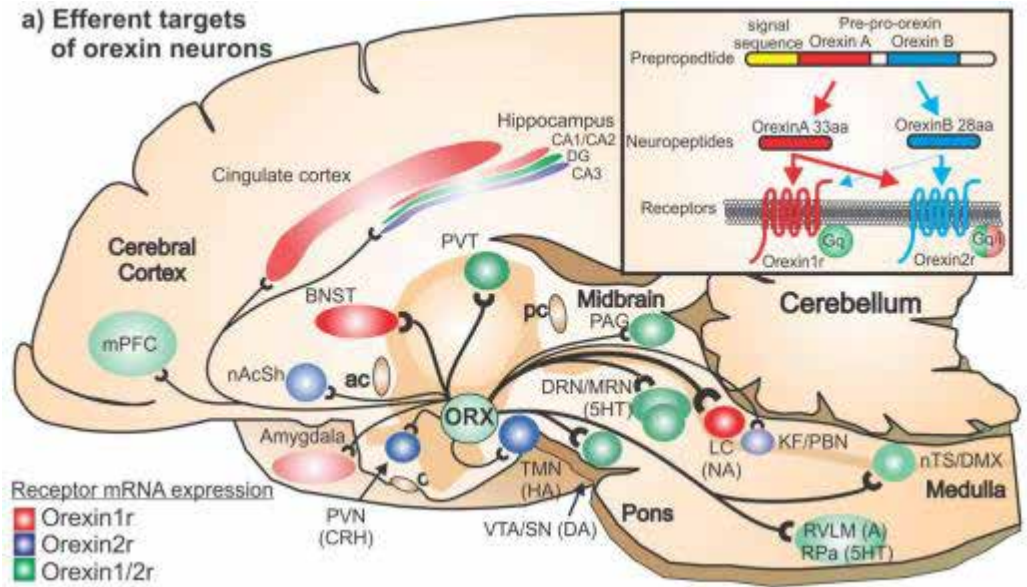
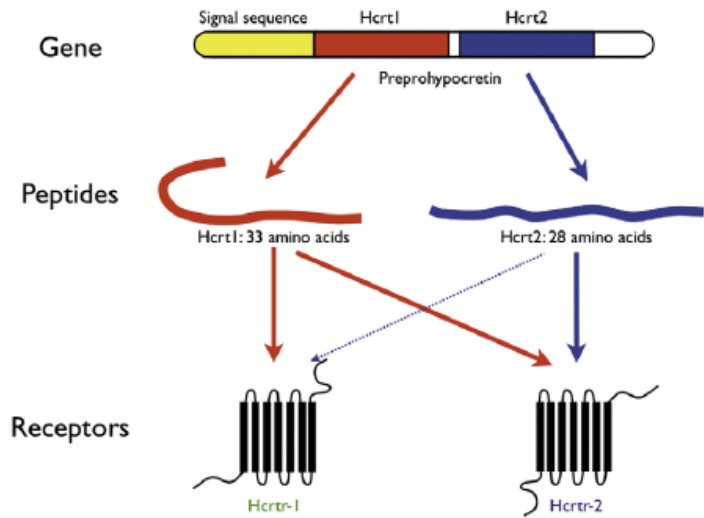


Fernando Berrendero

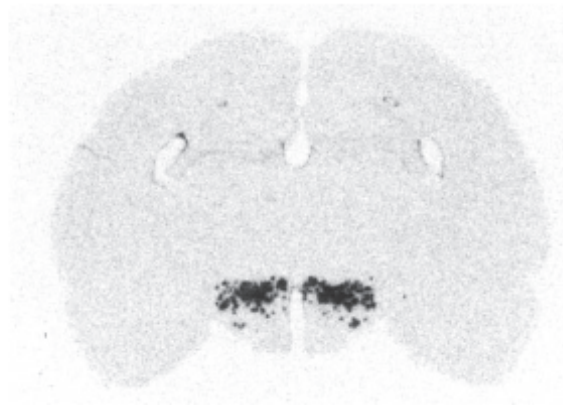
Laboratorio de Neurofarmacología

Dpto. de Ciencias Experimentales y de la Salud, UPF

The hypocretin/orexin system



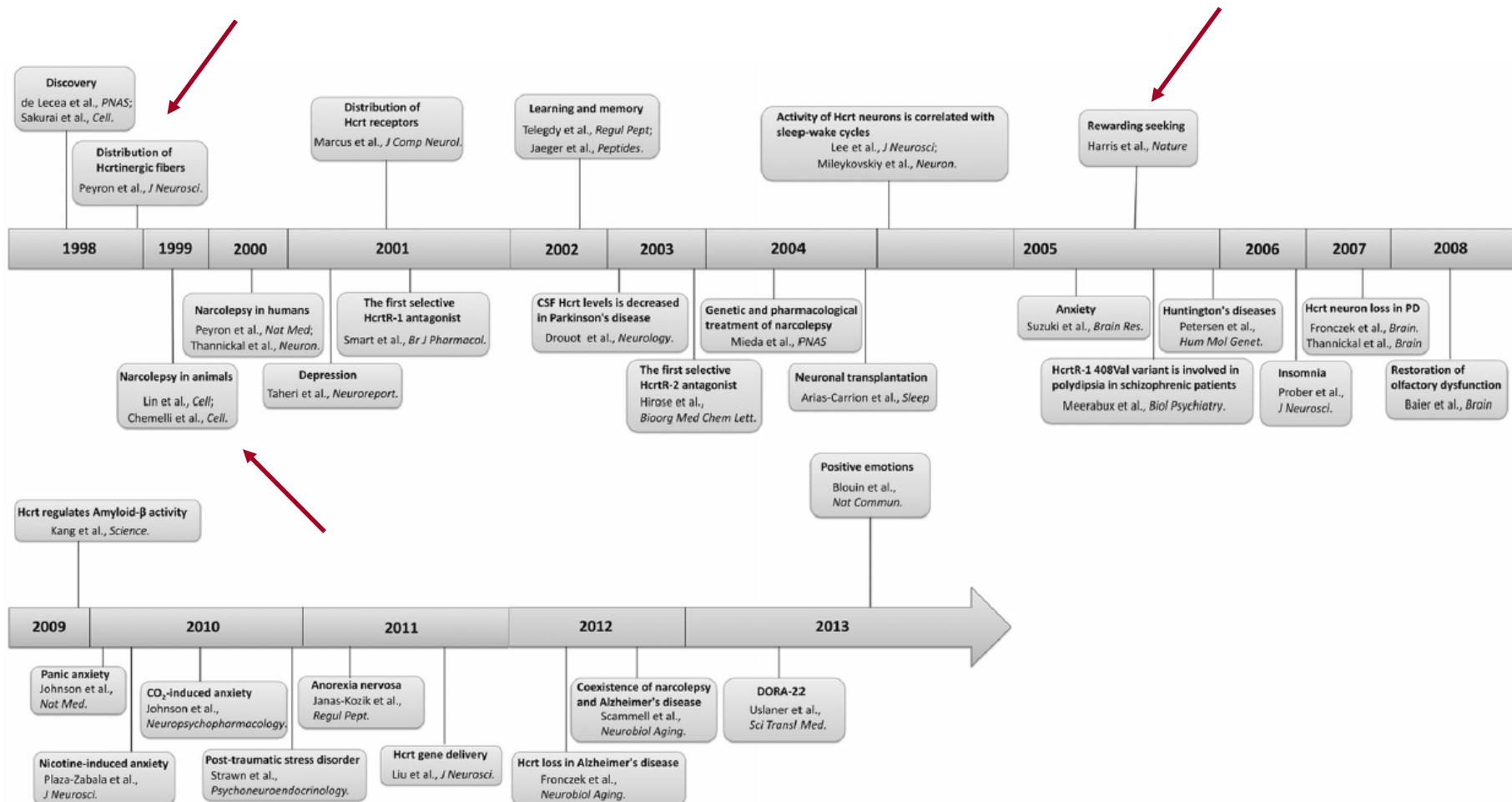
Johnson et al, *Prog Brain Res*, 2012



Diverse physiological functions:

- Arousal and sleep/wake cycles
- Food intake and energy homeostasis
- Emotional behavior and stress
- Reward and addiction**

Chronicle of events about the role of the hypocretin/orexin system in neuropsychiatry



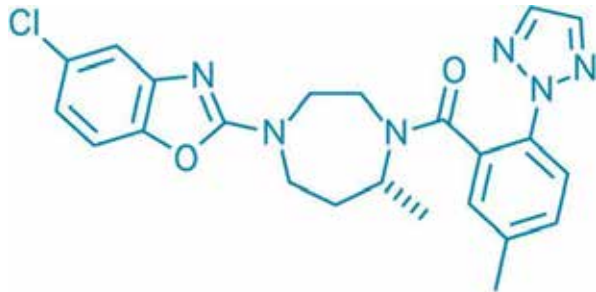
NEWS & ANALYSIS

First-in-class insomnia drug on the brink of approval nod

Merck's dual orexin receptor antagonist suvorexant is approaching the regulatory finish line, 15 years after orexins were discovered.



Osborne, *Nat Rev Drug Discov*, 2013



MK-4305: 2006–11
Suvorexant: 2011–

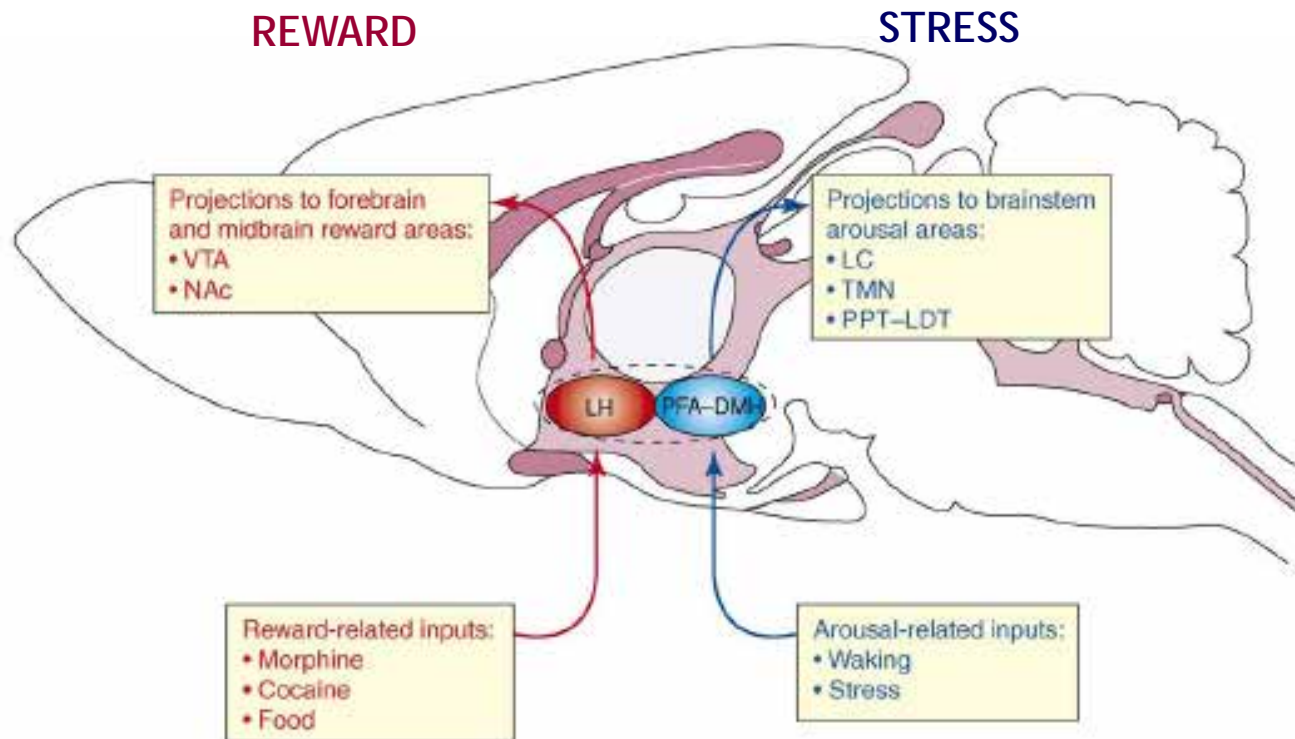
Company: **Merck & Co.**

Indication: **Insomnia**

Target: **Orexin receptors 1 & 2**



The hypocretin/orexin system



Harris and Aston-Jones, *Trends Neurosci*, 2006

Hallmarks of tobacco addiction

- **Compulsive** tobacco use
- **Loss of control** over tobacco consumption despite its harmful effects
- The appearance of **withdrawal** symptoms upon smoking cessation
- **Relapse** after long periods of abstinence

80% of smokers who attempt to quit on their own relapse within the first month of abstinence (Benowitz, 2010)

Three factors facilitate relapse:

- **Stress**
- Environmental **cues**
- **Re-exposure** to tobacco

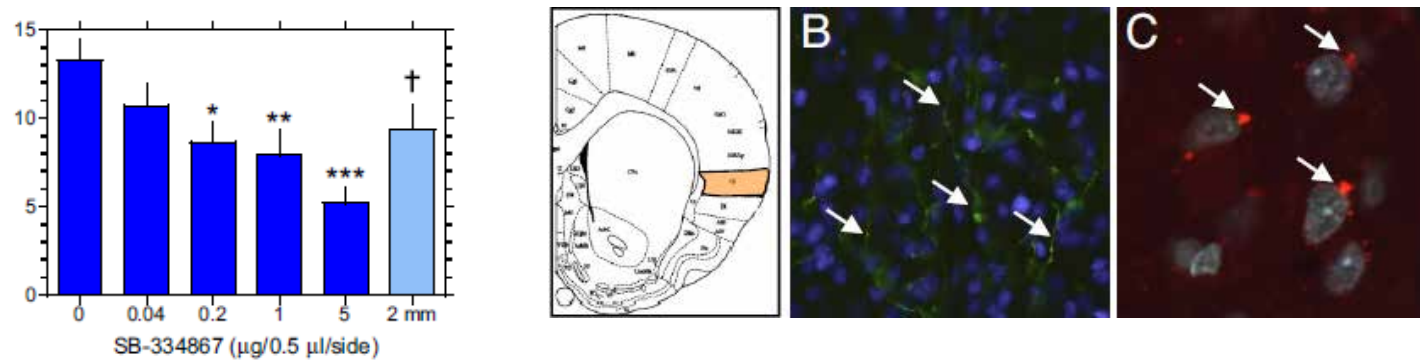


Insular hypocretin transmission regulates nicotine reward

Jonathan A. Hollander^a, Qun Lu^a, Michael D. Cameron^b, Theodore M. Kamenecka^b, and Paul J. Kenny^{a,1}

^aMolecular Therapeutics and ^bTranslational Research Institute, The Scripps Research Institute, Jupiter, FL 33458

19480–19485 | PNAS | December 9, 2008 | vol. 105 | no. 49



Damage to the Insula Disrupts Addiction to Cigarette Smoking

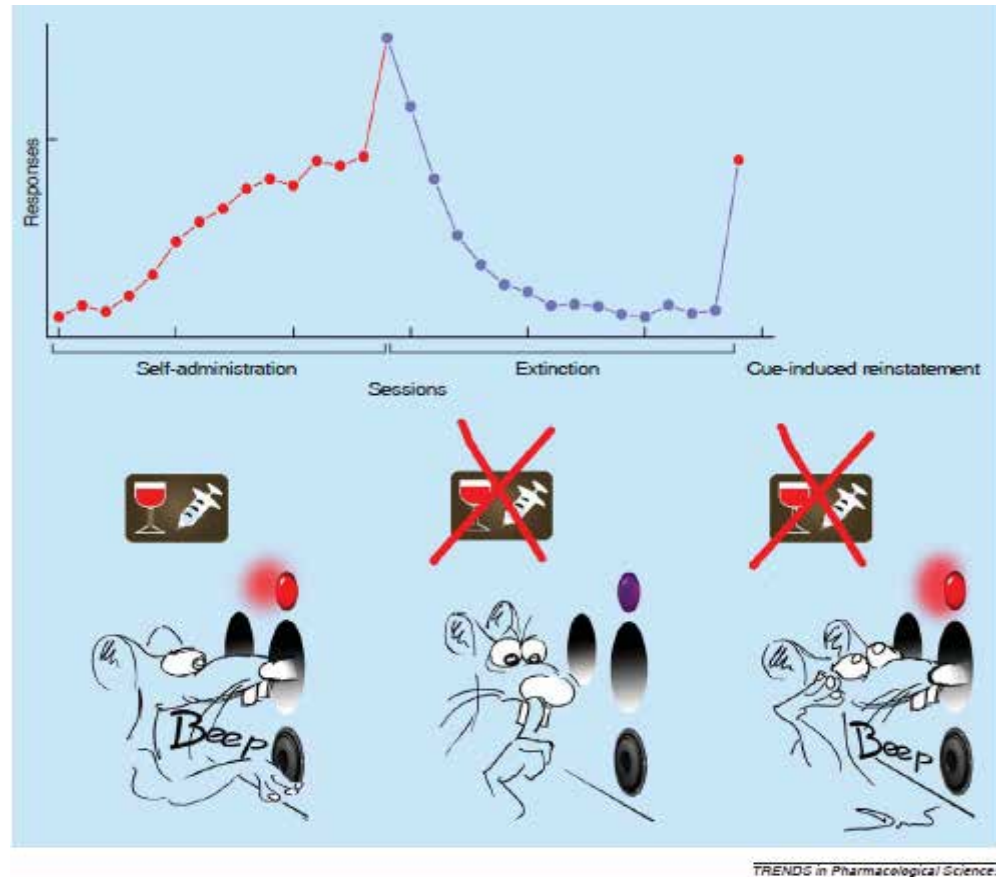
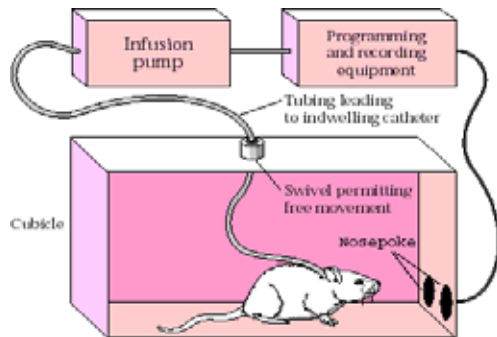
Nasir H. Naqvi,¹ David Rudrauf,^{1,2} Hanna Damasio,^{3,4} Antoine Bechara^{1,3,4,*}

SCIENCE VOL 315 26 JANUARY 2007

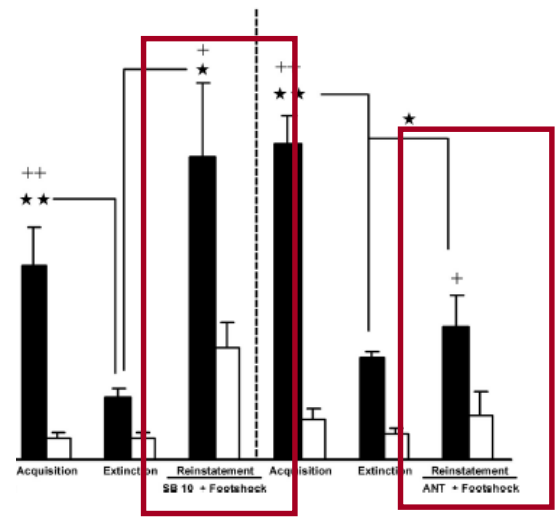
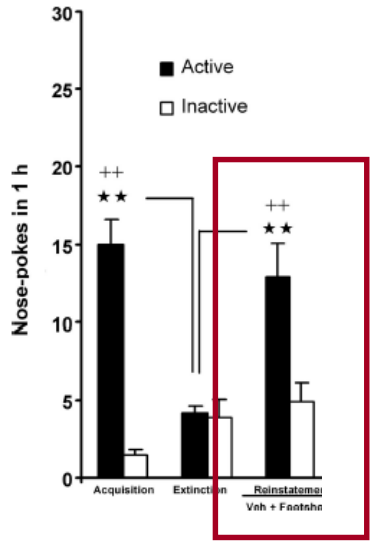
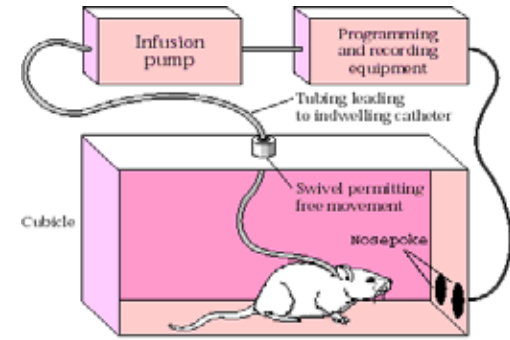
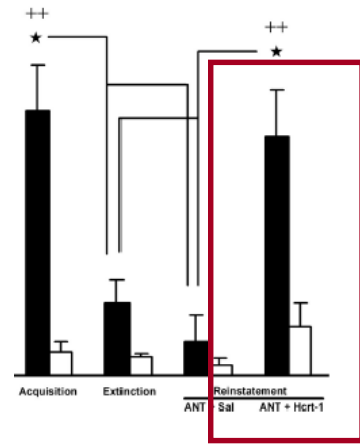
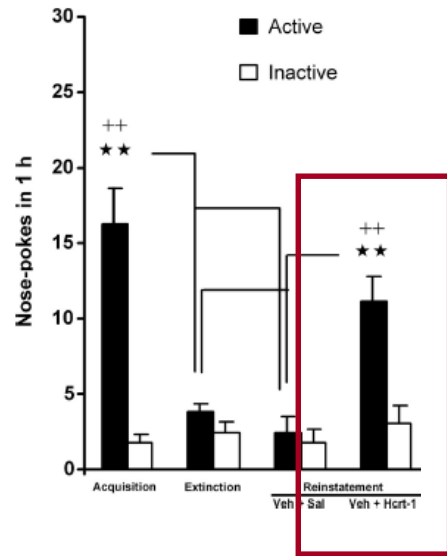
Intravenous drug self-administration model

3 phases:

- 1.Acquisition
- 2.Extinction
- 3.Reinstatement



ARE HYPOCRETINS INVOLVED IN STRESS-INDUCED REINSTATEMENT OF NICOTINE-SEEKING BEHAVIOUR?



Hypocretin-1 (icv)



Hcrtr-1



Reinstatement of nicotine-seeking behaviour

Footshock stress



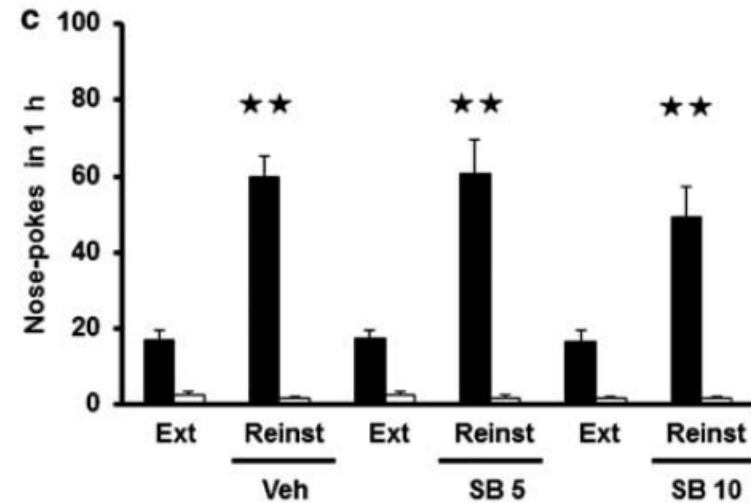
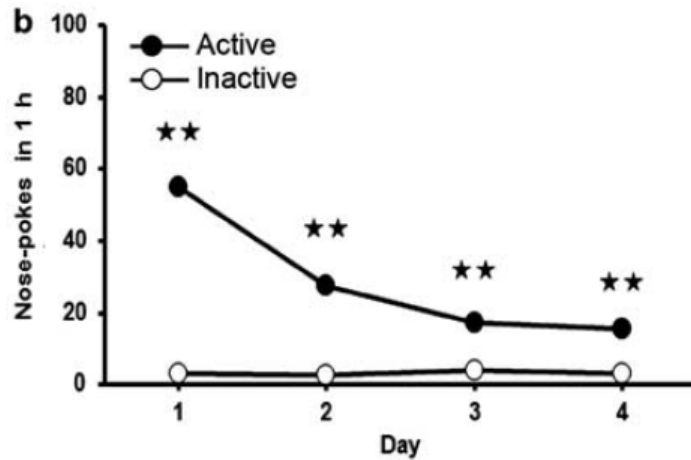
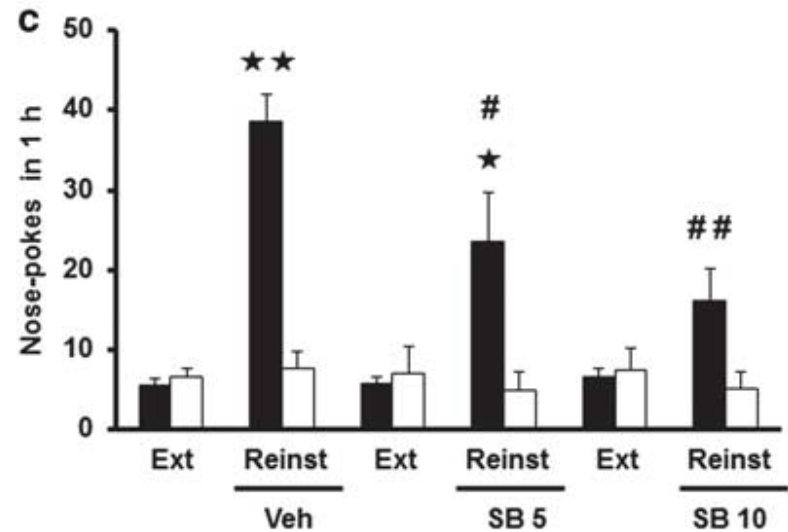
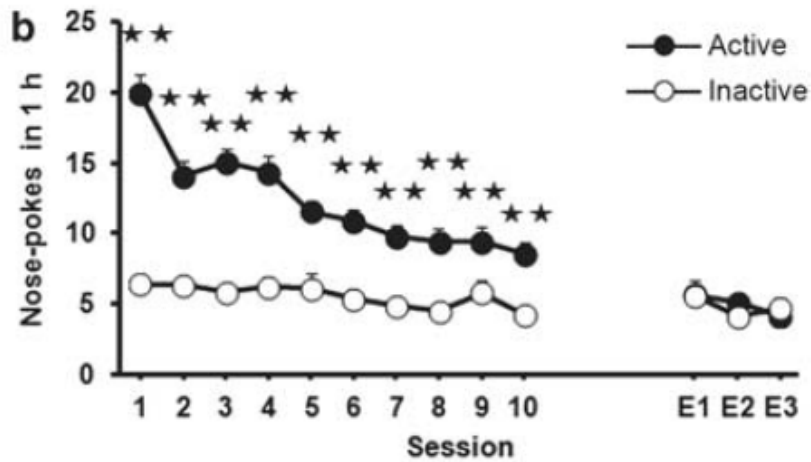
CRF1-R



1. ~~Stress~~

2. Nicotine-associated **cues**

3. **Nicotine** priming injection



Plaza-Zabala et al, *Neuropsychopharmacology*, 2013

HYPOCRETIN RECEPTOR-1 IS INVOLVED IN CUE-INDUCED REINSTATEMENT OF NICOTINE-SEEKING BEHAVIOUR

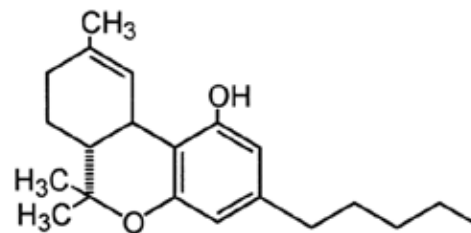
ü **Cannabis** is the most widely **used illicit drug** in the world

ü Although there is a high prevalence of users who seek treatment for **cannabis** dependence, **no accepted pharmacologic treatment** is available to facilitate and maintain abstinence

ü The **hypocretin/orexin system** plays a critical role in drug addiction, but the potential **participation** of this system in the **addictive** properties of **cannabinoids** is **unknown**



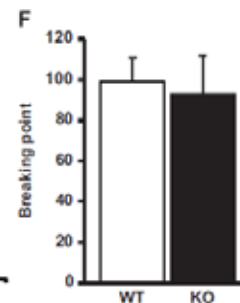
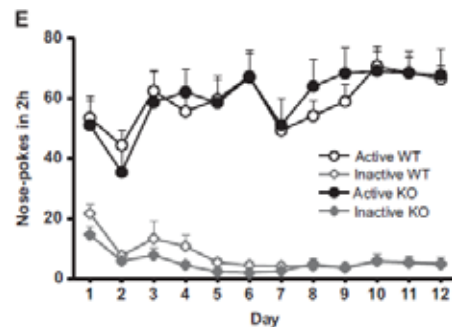
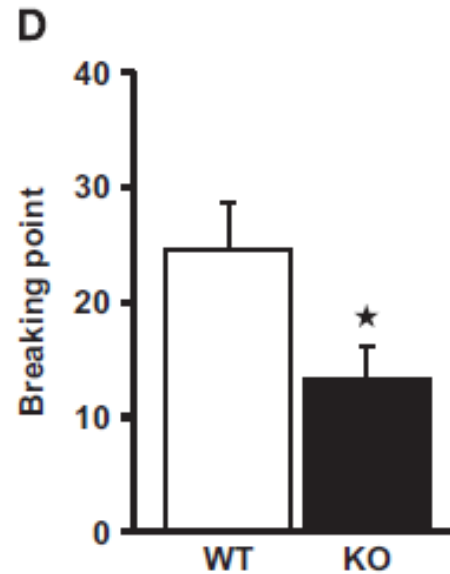
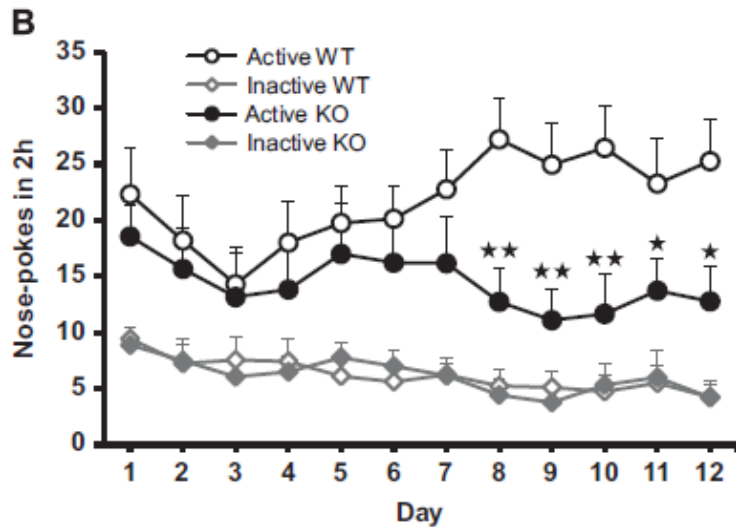
Cannabis sativa



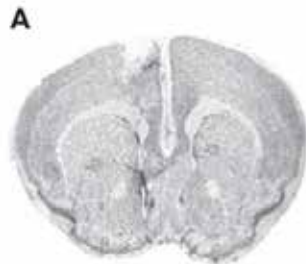
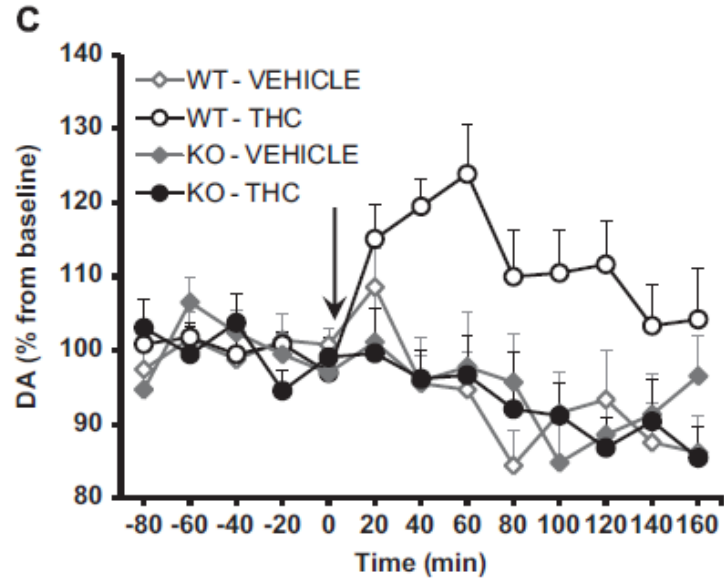
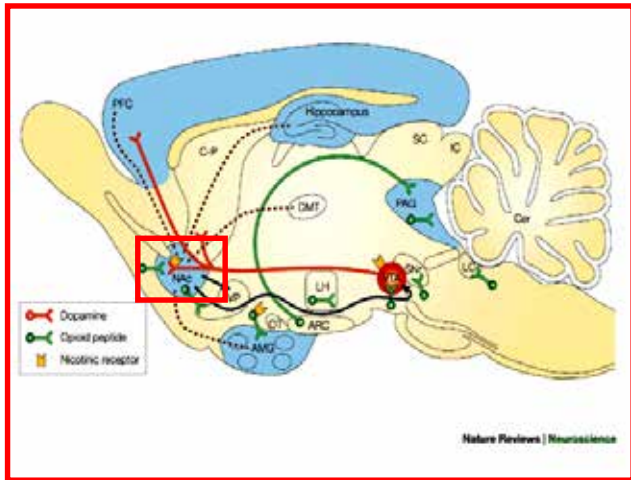
Δ -9-tetrahydrocannabinol (THC)

HYPOCRETIN RECEPTOR-1 IS INVOLVED IN THE REINFORCING PROPERTIES OF CANNABINOIDS

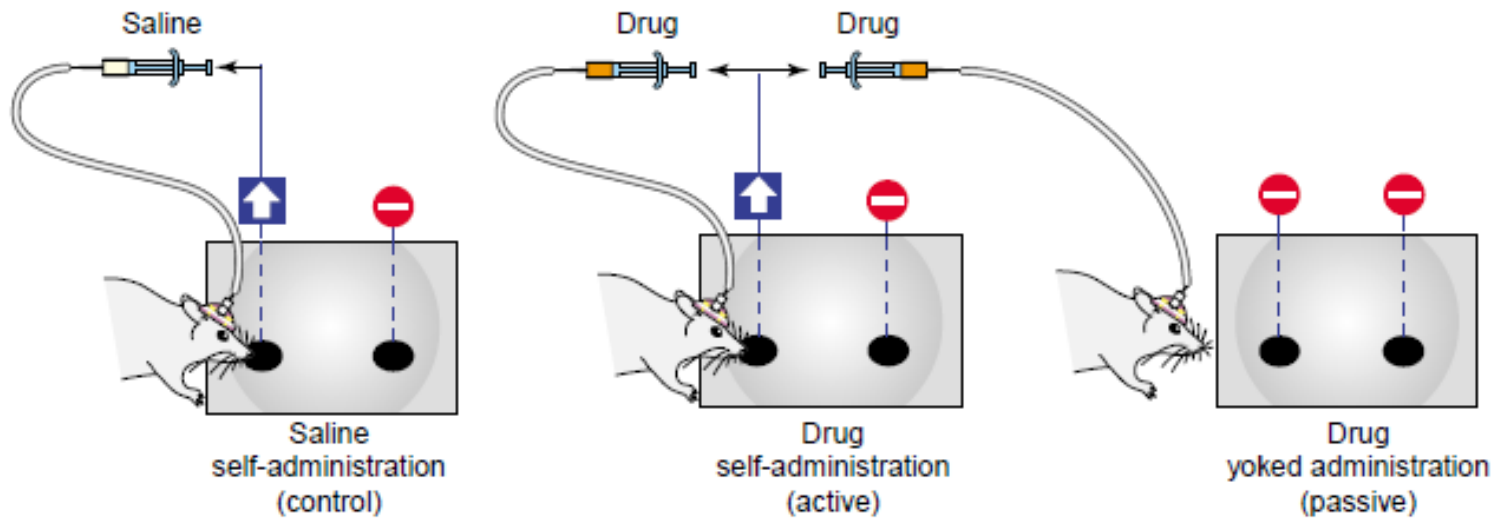
WIN 55,212-2 self-administration in WT and Hcrtr-1 KO mice



The Enhancement of Dopamine Extracellular Levels in the Nucleus Accumbens Induced by THC Is Blocked in Hypocretin Receptor-1 Knockout Mice

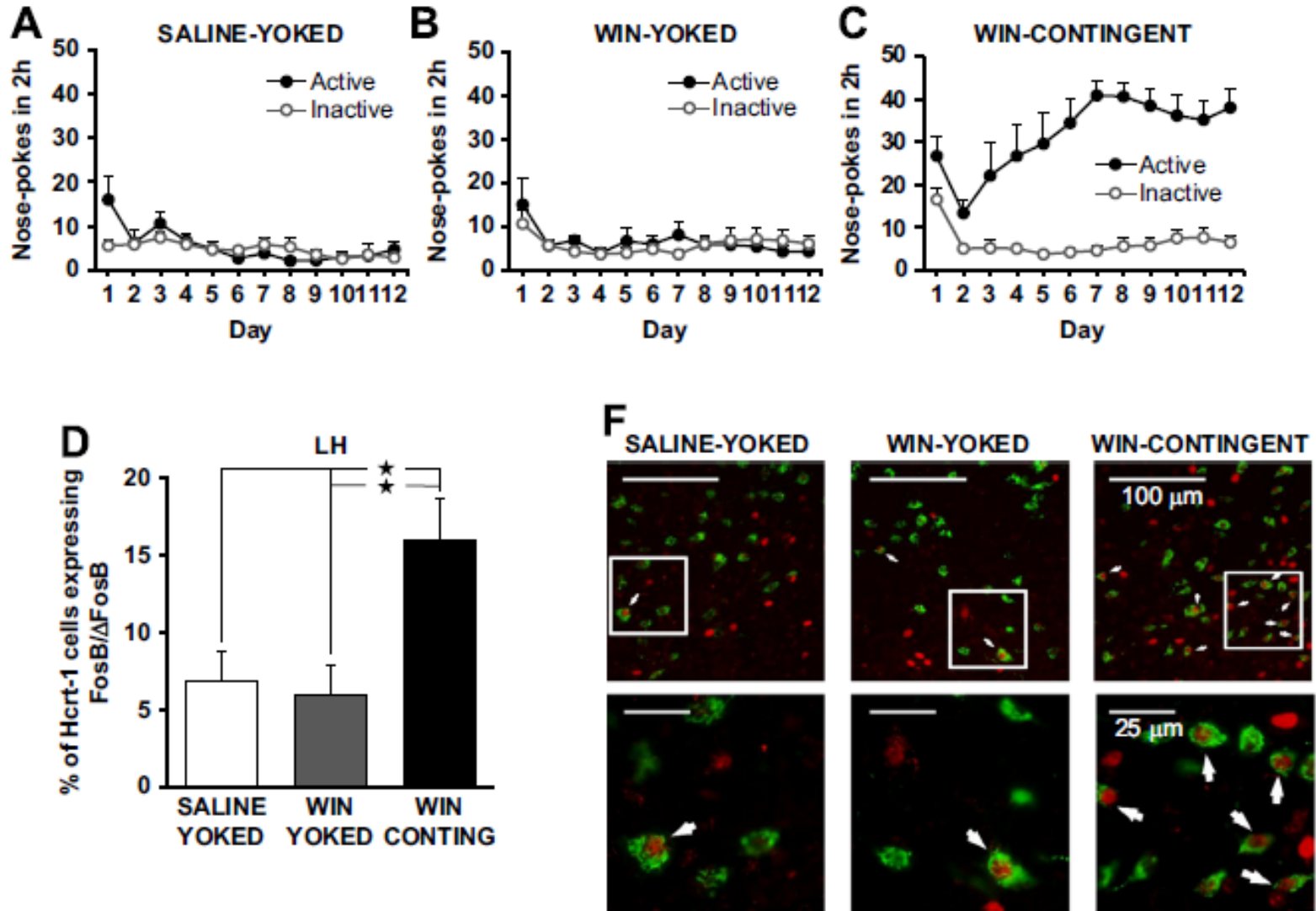


Yoked Control-Operant Model



TRENDS in Pharmacological Sciences

Immunofluorescence of FosB/DFosB with hypocretin-1










Hcrtr-1 antagonists could represent an interesting pharmacologic tool for...

üthe design of **new therapeutic strategies** to achieve **smoking cessation**

ücannabis **dependence** in humans, which is a major clinical need devoid of available treatment at the present moment

Summary of orexin/hypocretin roles in addiction

	Cocaine	Nicotine	Opiates	Ethanol	Food
Acute withdrawal 		↓	↓		
Sensitization 	↓				
Conditioned place preference 	↓ / No effect		↓	No effect	
Self-administration 	No effect	↓	↓	↓	↓ / No effect
Fixed ratio Progressive ratio	↓	↓	↓	↓	↓ / No effect
Cue-induced reinstatement 	↓		↓	↓	↓ / No effect
Stress-induced reinstatement 	↓	No effect		↓	↓ / No effect
Prime-induced reinstatement 	No effect		No effect		No effect

Agradecimientos



Ainhoa Plaza-Zabala



África Flores



"Una manera de hacer Europa"

LABORATORIO DE NEUROFARMACOLOGÍA, CEXS-UPF



Muchas

Gracias!!