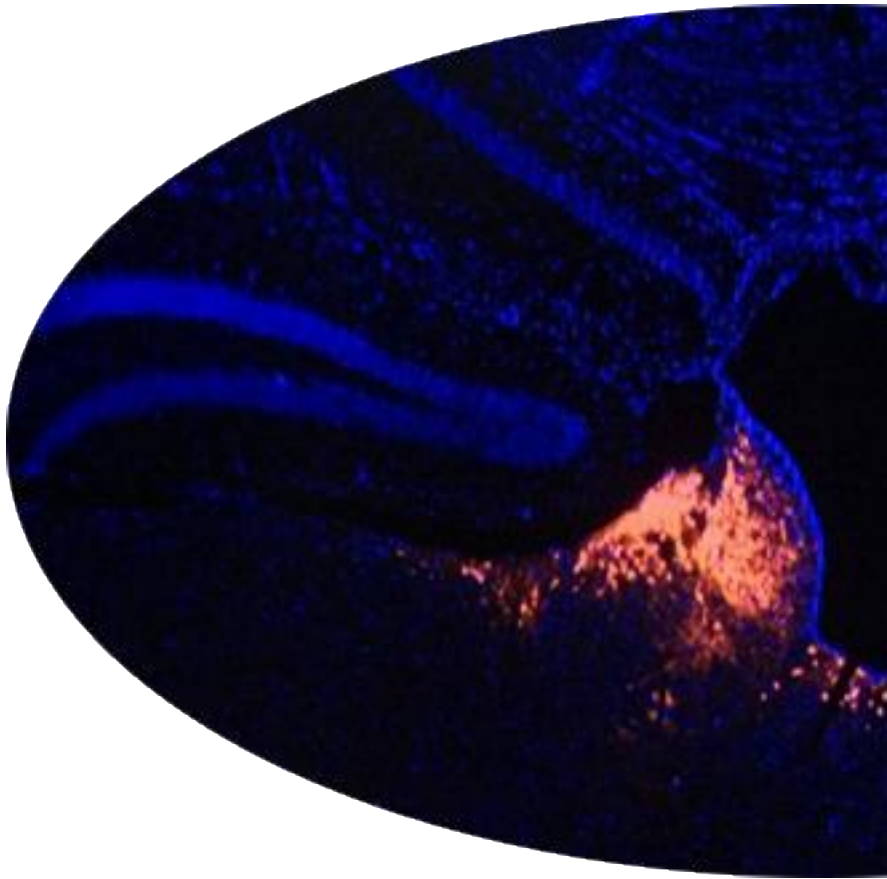
CRBS Centre de recherche en biomédecine de Strasbourg
Université de Strasbourg
Inserm

ADDICTIONS TEAM
Lalanne & Darcq Lab

Développement de nouvelles molécules en préclinique



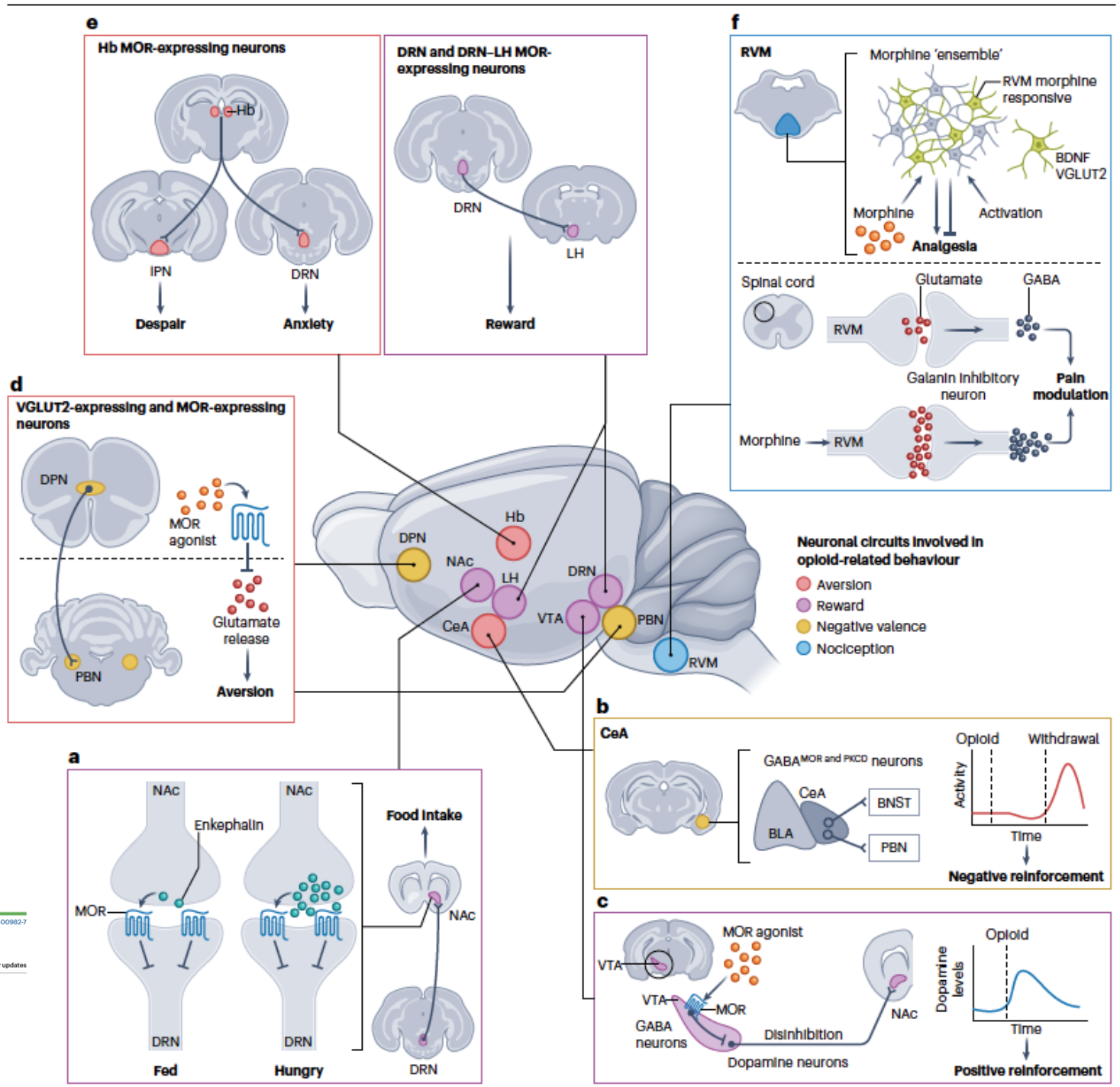
Emmanuel Darcq, PhD

INSERM, France
Strasbourg Translational Neuroscience & Psychiatry (INSERM U1329)
Addictions Team

2025 **Pharmacopsy Alsace / Erstein**

nature reviews neuroscience
https://doi.org/10.1038/s41583-025-00982-7
Review article
Check for updates

The neural circuits and signalling pathways of opioid use disorder



Mathis, Ehrlich and Darcq 2025 Nat Rev Neuro

nature reviews neuroscience
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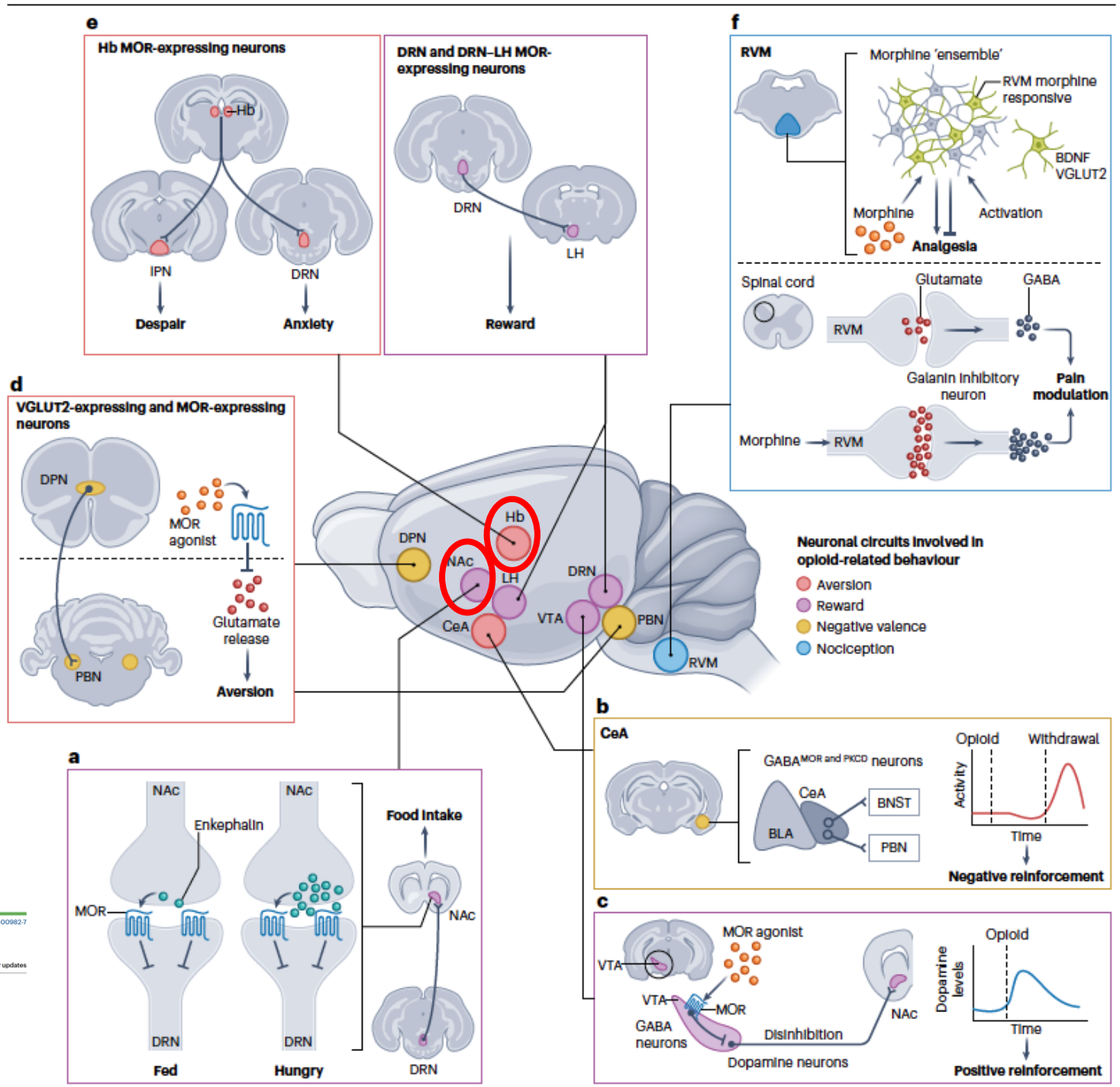
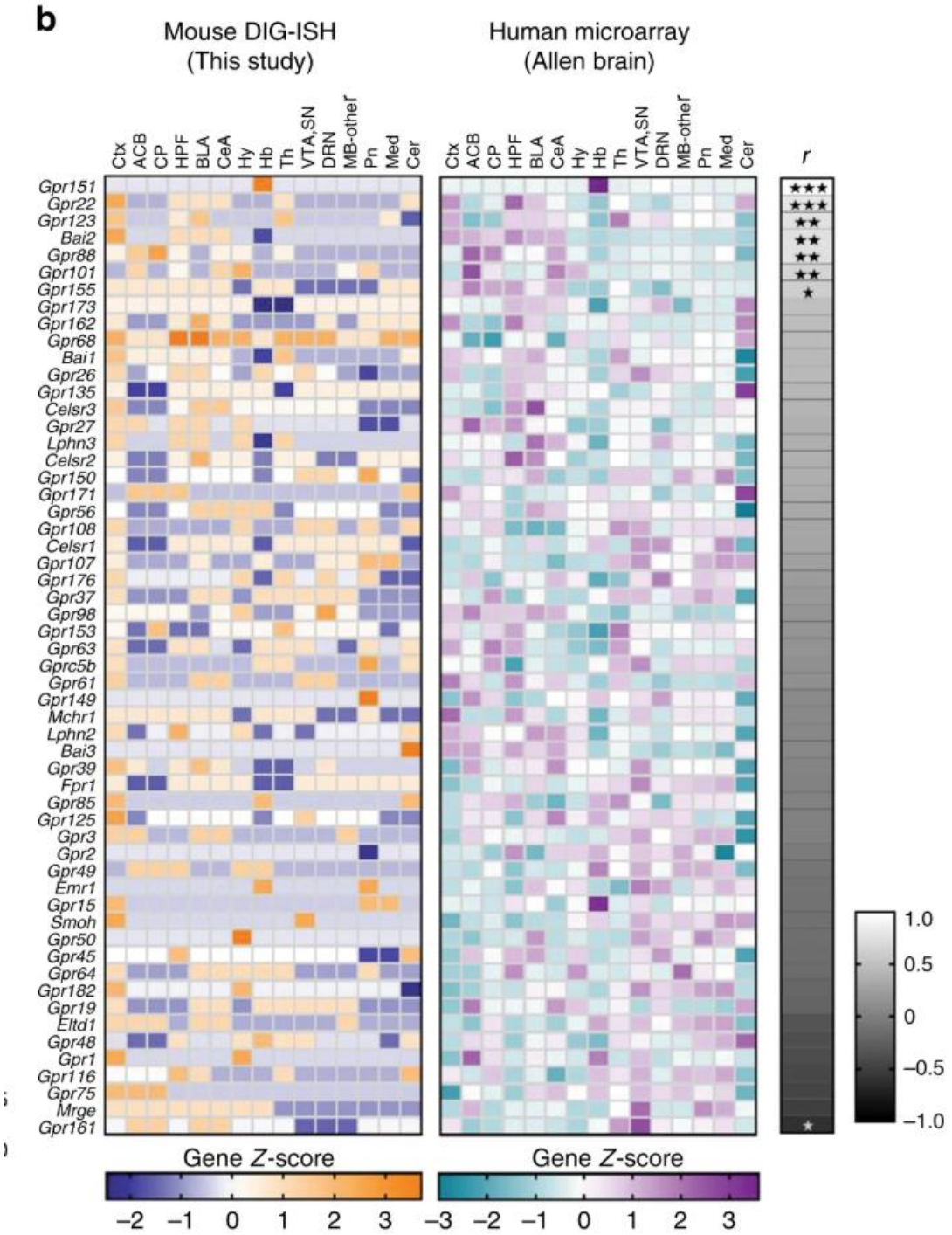
The neural circuits and signalling pathways of opioid use disorder



Mathis, Ehrlich and Darcq
2025 Nat Rev Neuro

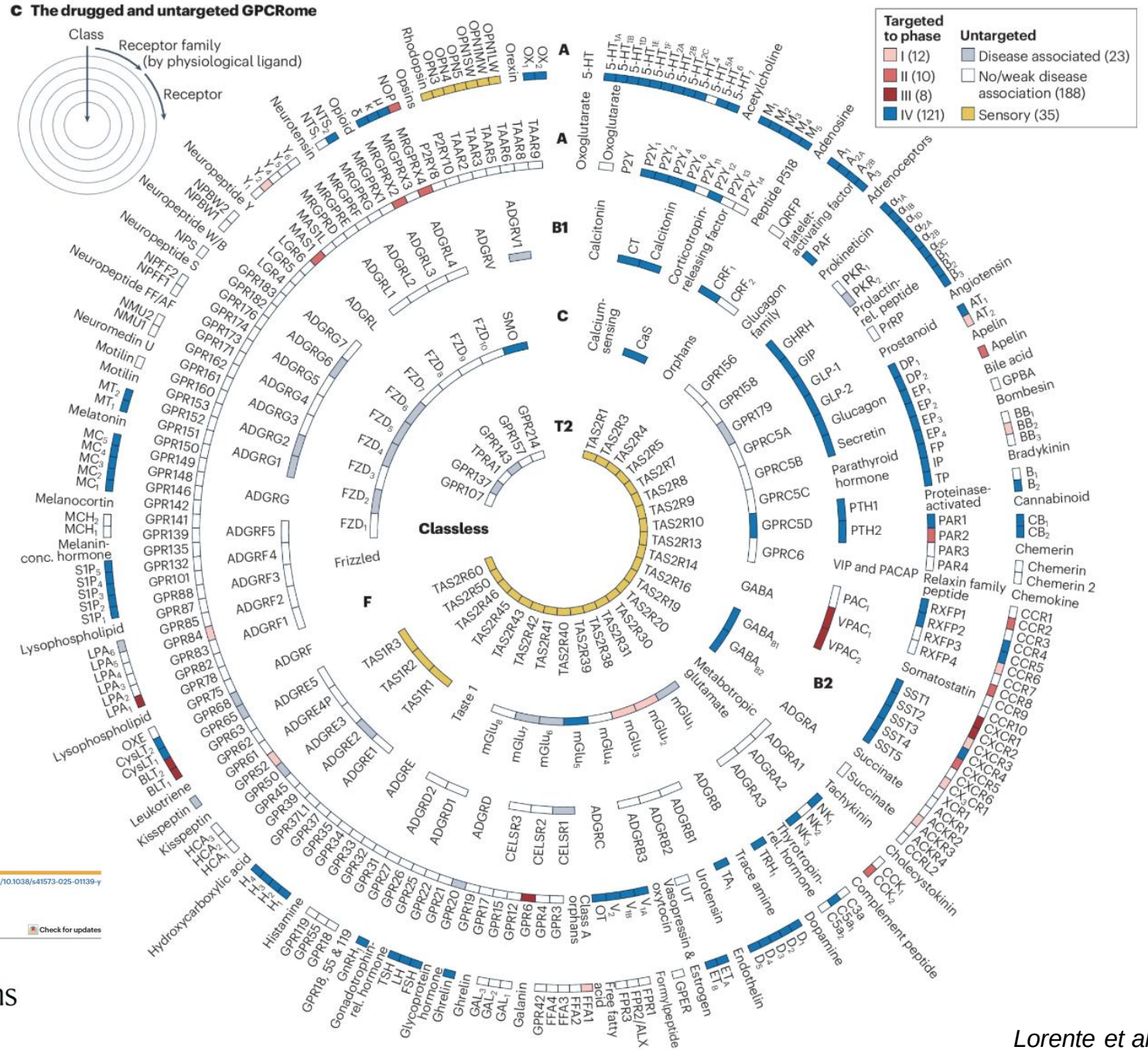


A. Erhlich

B. Kieffer

Ehrlich et al.
2018 Communication Biology

« 516 approved drugs targeting GPCRs, making up 36% of all approved drugs »



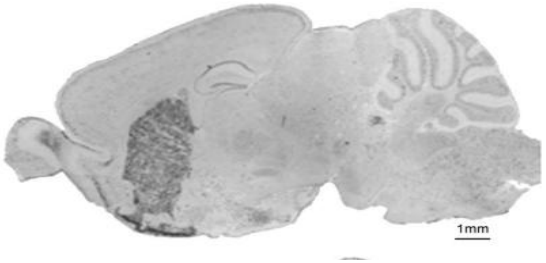
nature reviews drug discovery
https://doi.org/10.1038/s41573-025-01139-y
Review article
Check for updates

GPCR drug discovery: new agents, targets and indications

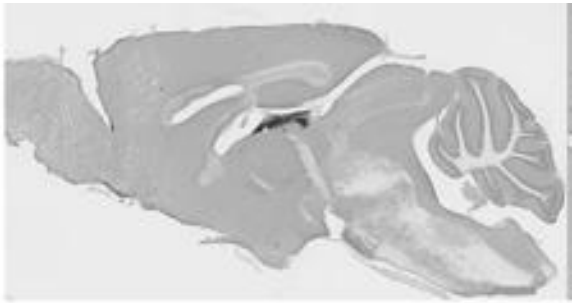
Lorente et al, 2025 Nat Rev Drug Discovery

2 récepteurs RCPG orphelin

- **GPR88 et striatum**



- **GPR139 et habénula**



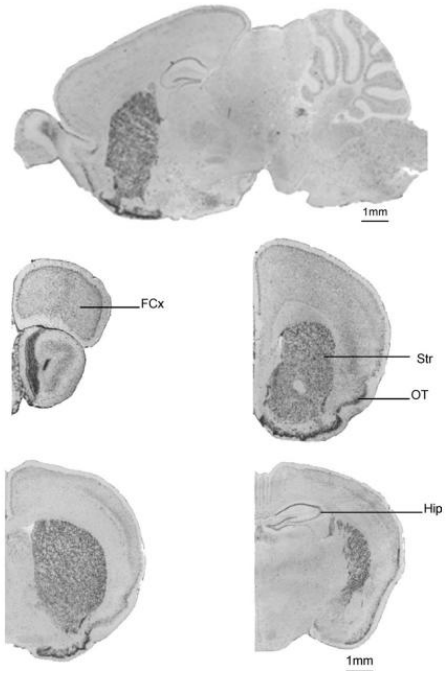
GPR88

Neuroscience 146 (2007) 1182–1192

IDENTIFICATION OF NOVEL STRIATAL GENES BY EXPRESSION PROFILING IN ADULT MOUSE BRAIN

A. GHATE,[a] K. BEFORT,[a] J. A. J. BECKER,[a] D. FILLIOL,[a] C. BOLE-FEYSOT,[a] D. DEMEBELE,[a] B. JOST,[a] M. KOCH[b] AND B. L. KIEFFER[a]*

cell types or tissues. Transcriptome analysis of the mammalian brain is a major goal of modern neurobiology to decipher molecular bases of cerebral functioning



Neuroscience 156 (2008) 950–965

TRANSCRIPTOME ANALYSIS IDENTIFIES GENES WITH ENRICHED EXPRESSION IN THE MOUSE CENTRAL EXTENDED AMYGDALA

J. A. J. BECKER,[a,b,c,d]* K. BEFORT,[a,b,c,d] C. BLAD,[a,b,c,d] D. FILLIOL,[a,b,c,d] A. GHATE,[a,b,c,d] D. DEMBELE,[e] C. THIBAULT,[e] M. KOCH,[e] J. MULLER,[f,g1] A. LARDENOIS,[f1] O. POCH[f] AND B. L. KIEFFER[a,b,c,d]

genes are predominantly expressed in brain. These genes encode signaling proteins (Adora2, GPR88, Arpp21 and Rem2), a transcription factor (Limh6) or proteins of unknown function (Rik130, Spata13 and Wfs1). The identification of

EJN European Journal of Neuroscience

European Journal of Neuroscience, Vol. 27, pp. 2973–2984, 2008 doi:10.1111/j.1460-9568.2008.06273.x

Mu-opioid receptor activation induces transcriptional plasticity in the central extended amygdala

K. Befort,[1] D. Filliol,[1] A. Ghate,[1] E. Darcq,[1] A. Matifas,[1] J. Muller,[2,3,4] A. Lardenois,[2,5] C. Thibault,[6] D. Dembele,[6] J. Le Merrer,[1] J. A. J. Becker,[1] O. Poch[2] and B. L. Kieffer[1]

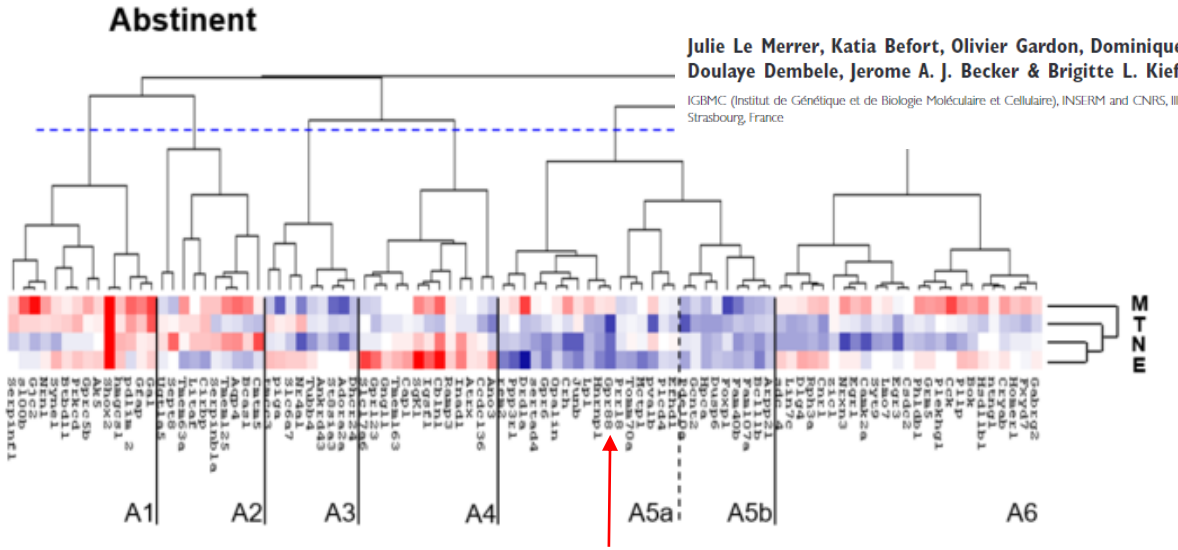
Addiction Biology

PRECLINICAL STUDY doi:10.1111/j.1369-1600.2011.00365.x

Protracted abstinence from distinct drugs of abuse shows regulation of a common gene network

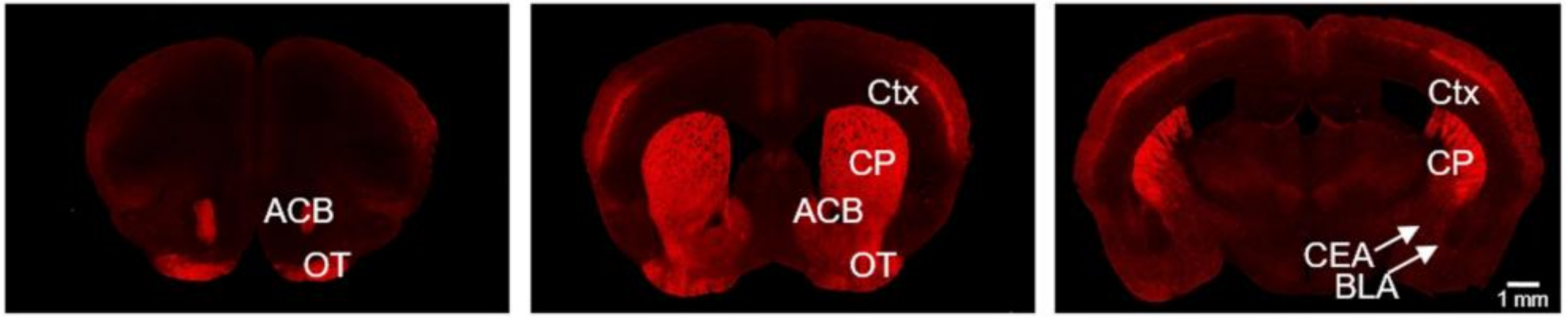
Julie Le Merrer, Katia Befort, Olivier Gardon, Dominique Filliol, Emmanuel Darcq, Doulaye Dembele, Jerome A. J. Becker & Brigitte L. Kieffer

IGBMC (Institut de Génétique et de Biologie Moléculaire et Cellulaire), INSERM and CNRS, Illkirch-Graffenstaden, France and UdS (Université de Strasbourg), Strasbourg, France



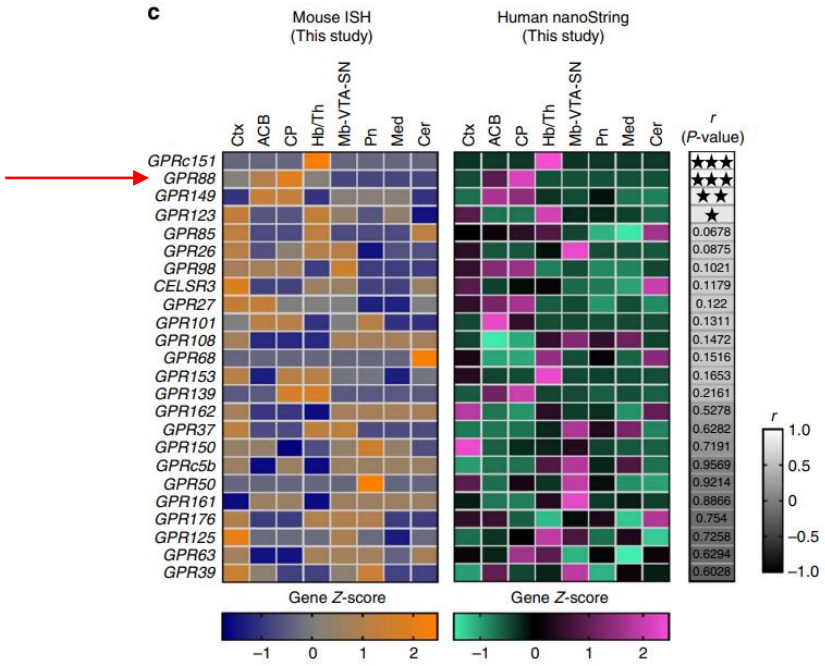
Gpr88 Distribution

In mice



Ehrlich et al Brain Structure and Function 2018

In Human



Ehrlich et al Com Biology 2018

Gpr88 agonist

Chunyang Jin, RTI, NC, USA

Journal of Medicinal Chemistry

Article

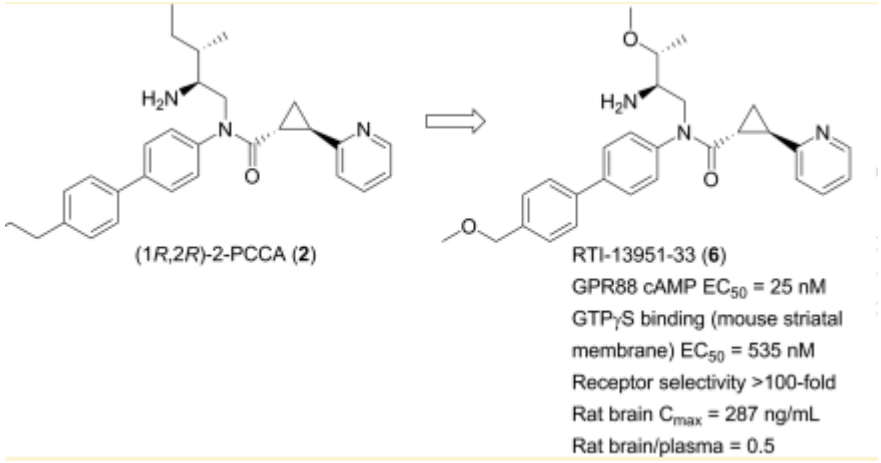
Cite This: J. Med. Chem. 2018, 61, 6748−6758

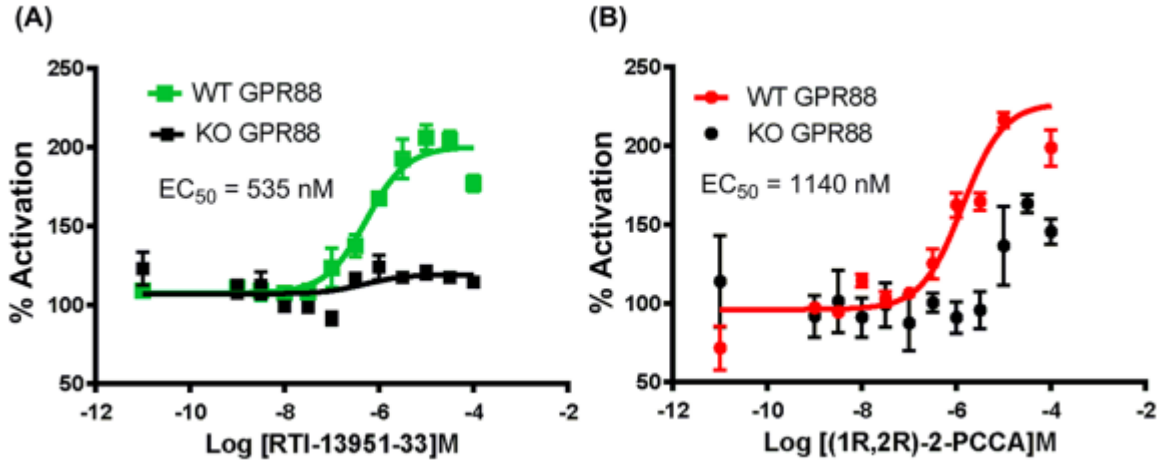
pubs.acs.org/jmc

Discovery of a Potent, Selective, and Brain-Penetrant Small Molecule that Activates the Orphan Receptor GPR88 and Reduces Alcohol Intake

Chunyang Jin,*[,†] Ann M. Decker,[†] Viren H. Makhijani,[‡] Joyce Besheer,[‡,#] Emmanuel Darcq,[§] Brigitte L. Kieffer,[§] and Rangan Maitra[†]

[†]Center for Drug Discovery, Research Triangle Institute, Research Triangle Park, North Carolina 27709, United States
[‡]Bowles Center for Alcohol Studies, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, United States
[#]Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, United States
[§]Department of Psychiatry, Douglas Mental Health Research Institute, McGill University, Montreal, Quebec H4H 1R3, Canada





Gpr88 agonist

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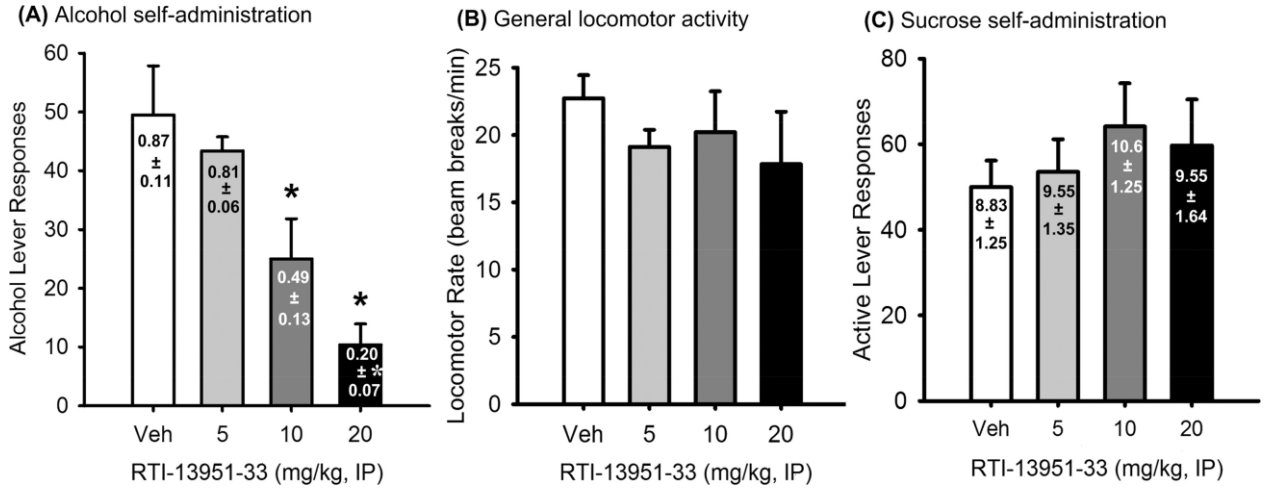
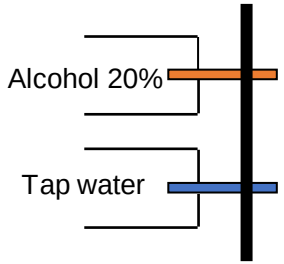


RTI33 reduces alcohol intake in intermittent access procedure

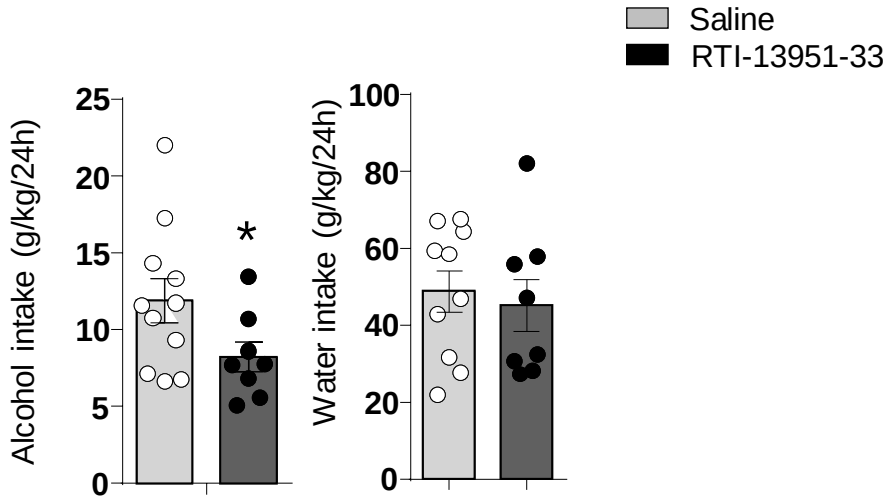
C57BL/6J mice
n=8-10

Intermittent-access 20% alcohol 2-bottle-choice drinking paradigm adapted from *Wise, 1973; Simms et al., 2008* :



24 hrs alcohol access on:

Monday
Wednesday
Friday



Mice underwent Intermittent access to 20% alcohol in a 2-bottle choice procedure for 8 weeks. Saline or RTI33 group assignments are then made in a pseudo-randomized manner to achieve similar pre-treatment alcohol intake.
Mice were injected with RTI-13951-33 (30 mg/kg, i.p) or Vehicle 30 minutes before the beginning of the last 24h alcohol drinking session. $p<0.05$. * vs Veh.

Improve Gpr88 agonist

Chunyang Jin, RTI, NC, USA

Journal of Medicinal Chemistry
pubs.acs.org/jmc Article

Design, Synthesis, and Structure–Activity Relationship Studies of (4-Alkoxyphenyl)glycinamides and Bioisosteric 1,3,4-Oxadiazoles as GPR88 Agonists

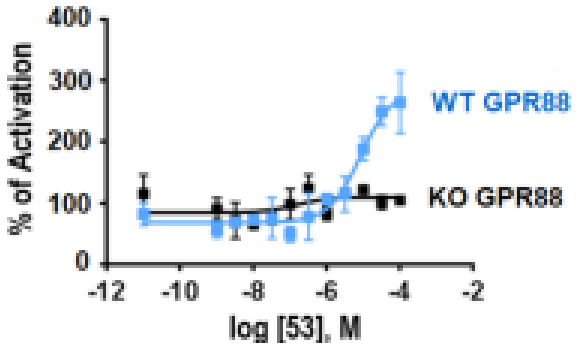
Md Toufiqur Rahman, Ann M. Decker, Tiffany L. Langston, Kelly M. Mathews, Lucas Laudermilk, Rangan Maitra, Weiya Ma, Emmanuel Darcq, Brigitte L. Kieffer, and Chunyang Jin*

Journal of Medicinal Chemistry
pubs.acs.org/jmc Article

Evaluation of Amide Bioisosteres Leading to 1,2,3-Triazole Containing Compounds as GPR88 Agonists: Design, Synthesis, and Structure–Activity Relationship Studies

Md Toufiqur Rahman, Ann M. Decker, Lucas Laudermilk, Rangan Maitra, Weiya Ma, Sami Ben Hamida, Emmanuel Darcq, Brigitte L. Kieffer, and Chunyang Jin*

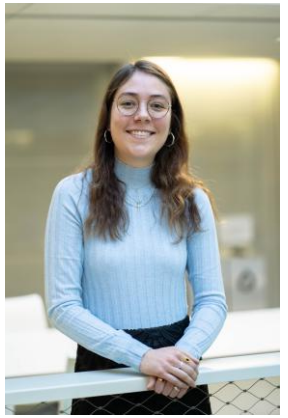
- **RTI-122**
  - ↗ Perméabilité cérébrale
  - ↗ ½ vie
  - ↗ Efficacité



			RTI-33	RTI-122
cAMP EC_{50} (nM)			45	12
solubility (μM)			412	261
Mouse PK (10 mg/kg, IP)	Plasma	C_{max} (ng/mL)	406	662
		t_{max} (h)	0.5	2
		$t_{1/2}$ (h)	0.7	5.8
		CL_F (mL/min/kg)	352	23
		$AUC_{0\text{-}inf}$ (ng/mL*h)		7292
	Brain	C_{max} (ng/mL)	178	630
		t_{max} (h)	0.5	4
		$t_{1/2}$ (h)		5.5
		CL_F (mL/min/kg)		20
		$AUC_{0\text{-}inf}$ (ng/mL*h)		8530
	Brain/Plasma		0.4	1.2

Cibler le récepteur orphelin GPR88 chez la souris pour limiter le trouble de l'usage d'opiacés

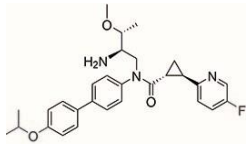
J. Meyer



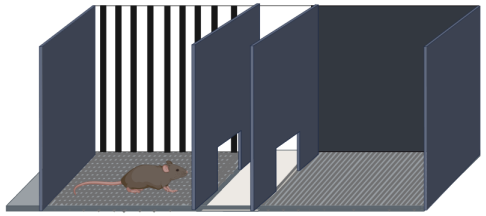
C. Tavenard

L'activation pharmacologique de GPR88 limite-elle le TUO ?

RTI-122
(Agoniste synthétique de GPR88)

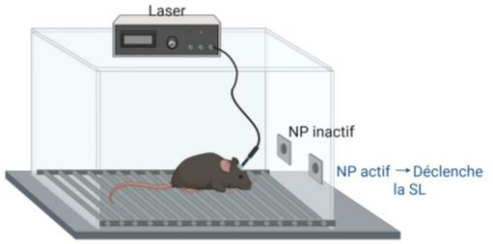


Effet **récompensant** de la morphine



Préférence de Place Conditionnée

Comportements de type **addictif**



Modèle d'auto-stimulation optogénétique

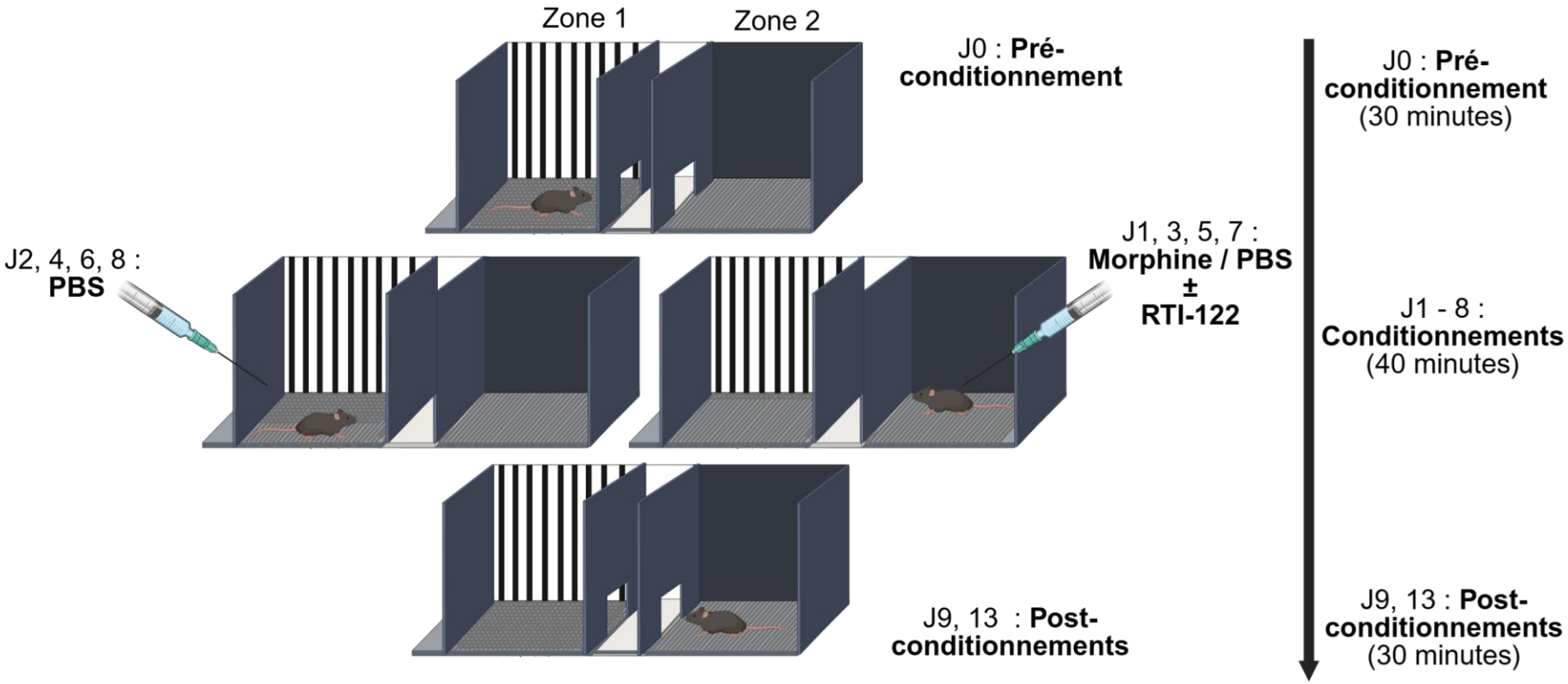
WT : Wild Type

Effet récompensant de la Morphine ± RTI-122

- Souris **WT** *vs* ***Gpr88* KO** *Meirsman et al. 2016*

→ GPR88

→ Ø GPR88

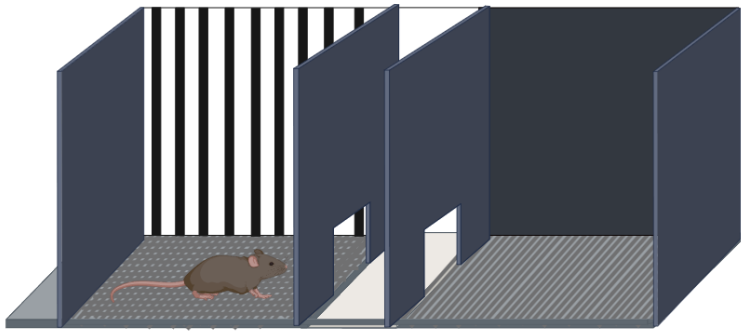


Préférence de Place Conditionnée

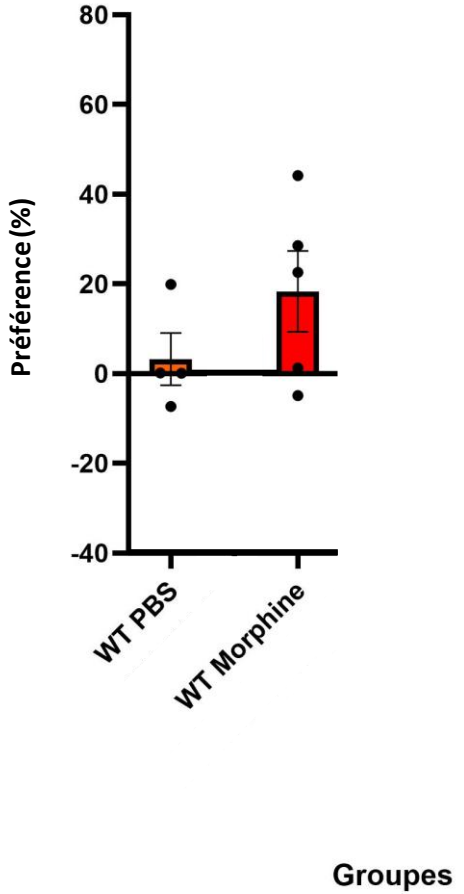
Effet récompensant de la Morphine

Morphine (10 mg/kg, i.p.)
RTI-122 (20 mg/kg, i.p.)

- Souris **WT**  → GPR88 *vs* ***Gpr88* KO**  → Ø GPR88



Préférence de Place Conditionnée

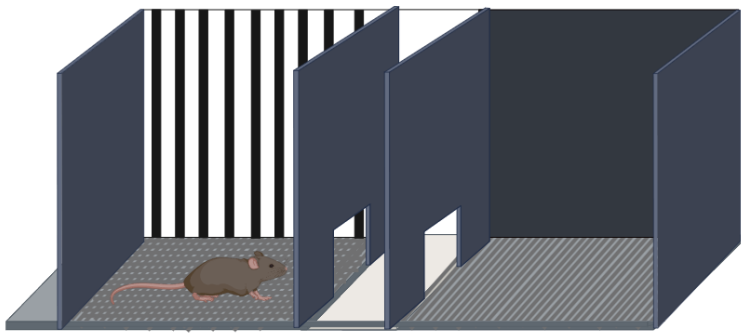


Test de Kruskal-Wallis (p = 0,52). n = 4-6/groupe. Moyenne ± S.E.M.

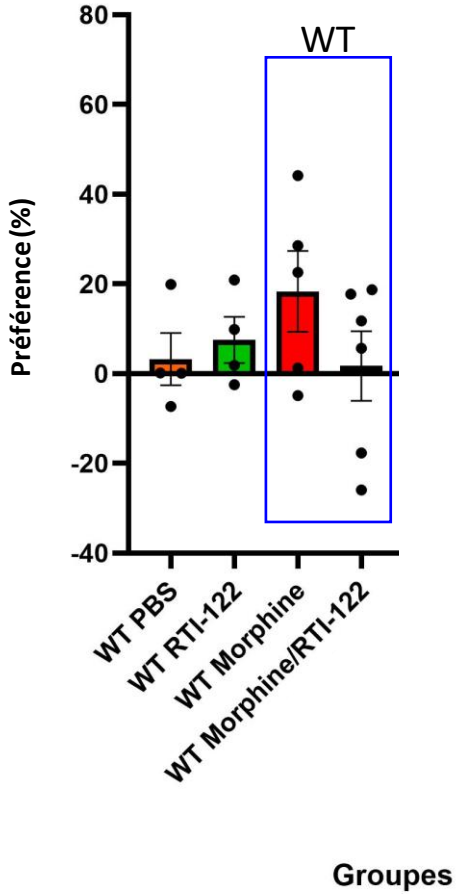
Effet récompensant de la Morphine ± RTI-122

Morphine (10 mg/kg, i.p.)
RTI-122 (20 mg/kg, i.p.)

- Souris **WT** → GPR88 *vs* ***Gpr88* KO** → Ø GPR88



Préférence de Place Conditionnée



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Morphine (10 mg/kg, i.p.)
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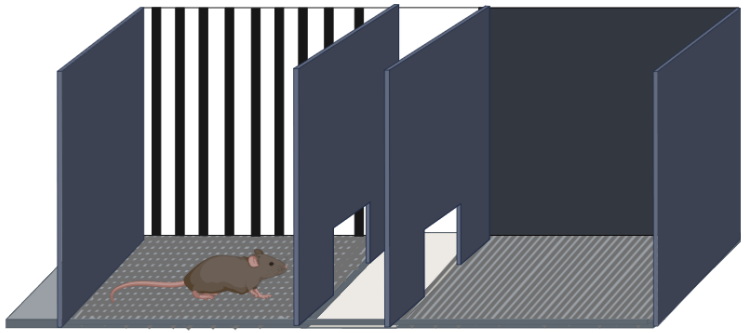
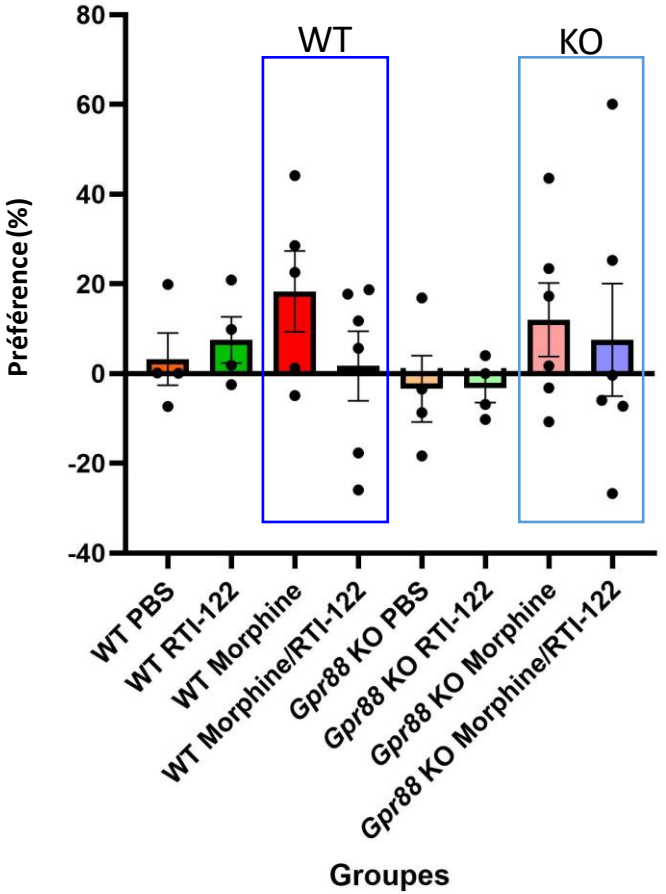


Préférence de Place Conditionnée

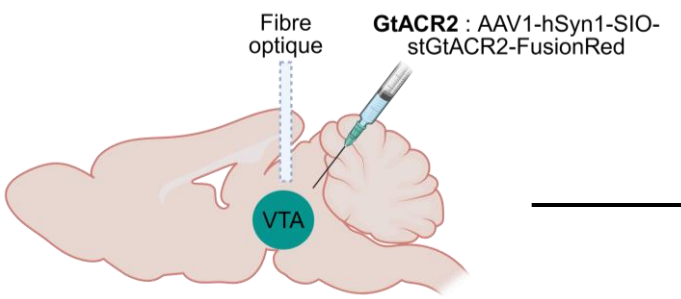


Test de Kruskal-Wallis (p = 0,52). n = 4-6/groupe. Moyenne ± S.E.M.

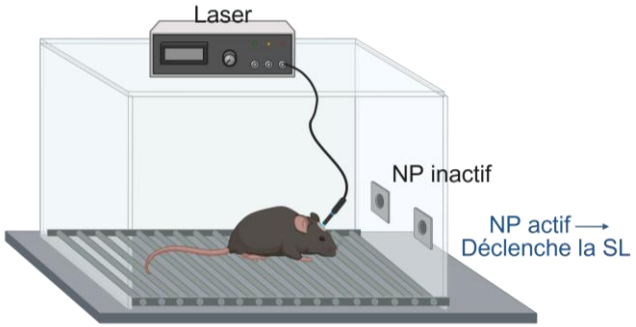
Comportements de type addictif ± RTI-122

MOR : Récepteur opioïde μ
NP : Nosepoke
VTA : Aire tegmentale ventrale

- Souris : MOR-Cre *Bailly et al. 2020*



Optogénétique



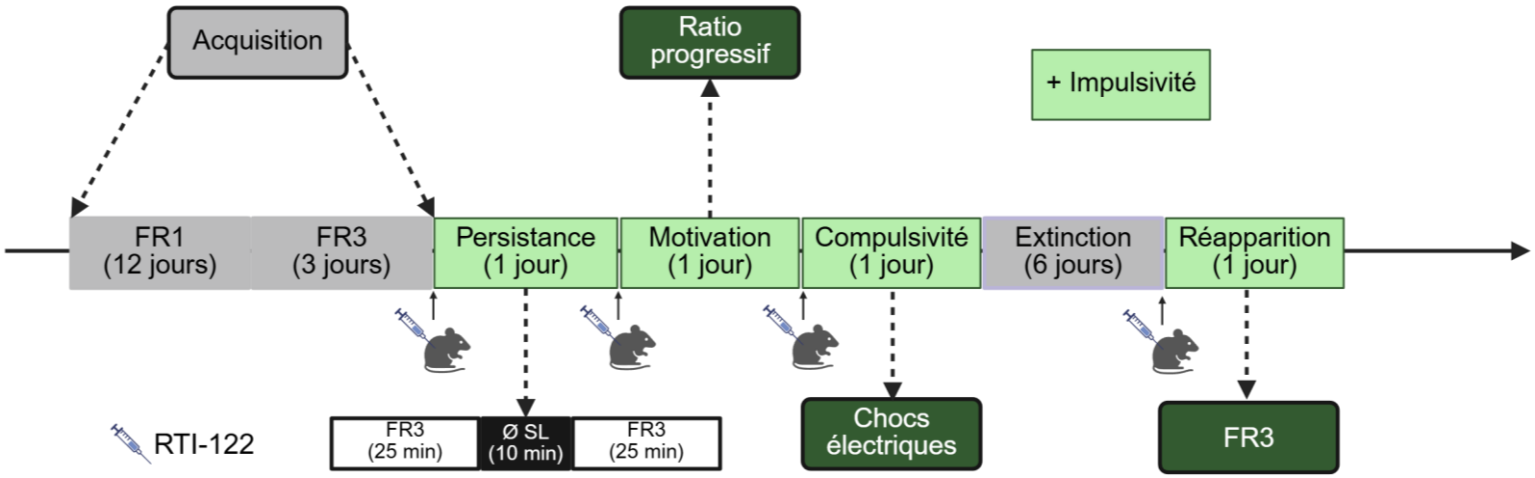
Modèle d'auto-administration de lumière

Opto-inhibition neurones MOR-VTA
→ Dopamine dans striatum

Johnson et al. 1992
Corre et al. 2018

- 5 comportements de type addictif

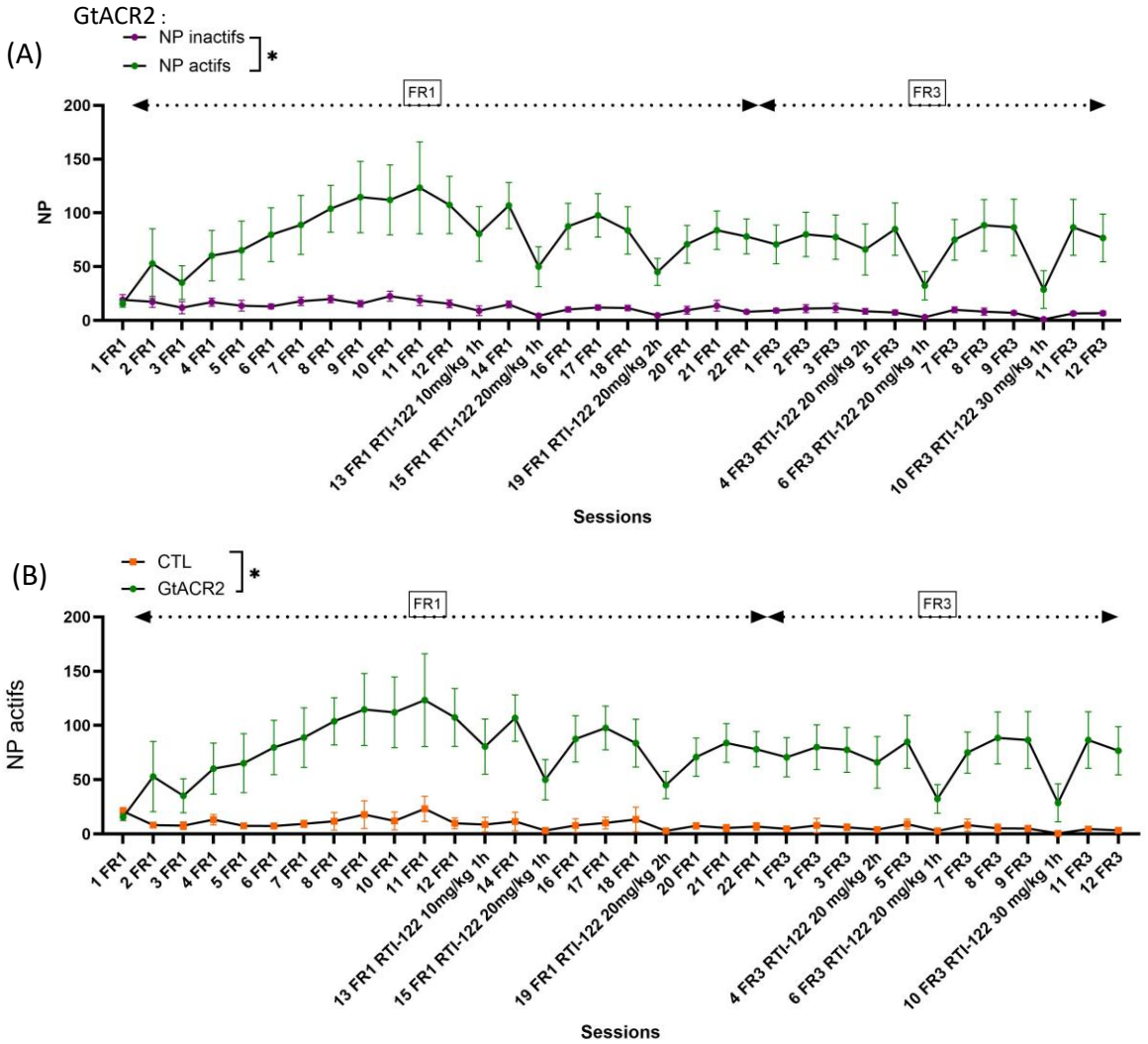
Deroche-Gamonet et al. 2004
Welsch et al. 2023



Comportements de type addictif ± RTI-122

NP : Nosepoke

Acquisition



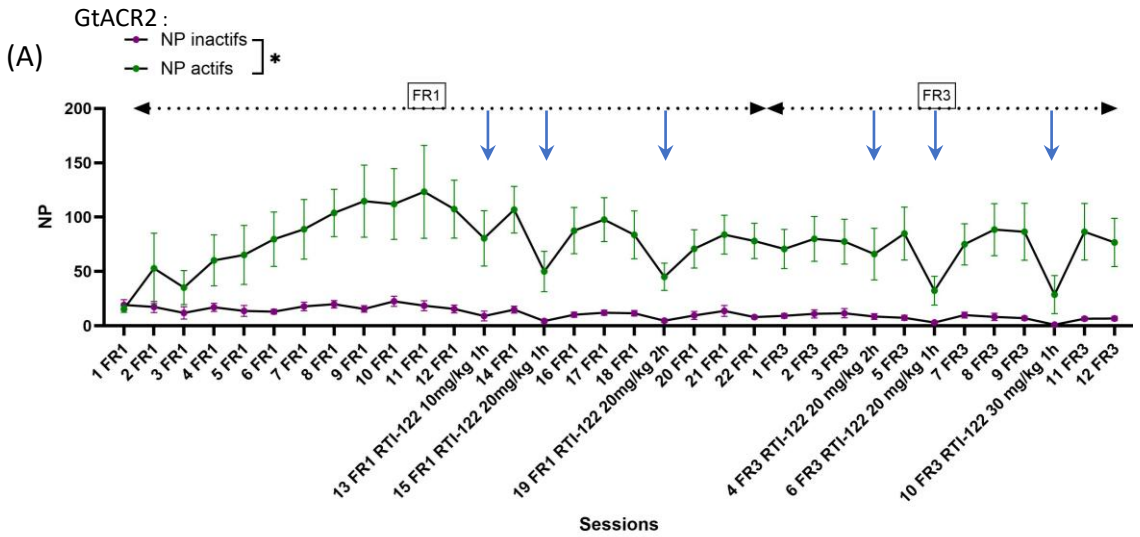
*(A, B) Test d'ANOVA à 2 facteurs à mesures répétées (A : p = 0,0102 ; B : p = 0,0147), test de comparaisons multiples de Tukey post-hoc. n = 6-8/groupe. Significativité statistique * : p < 0,05 ; ** : p < 0,01 ; *** : p < 0,001. Moyenne ± S.E.M.*

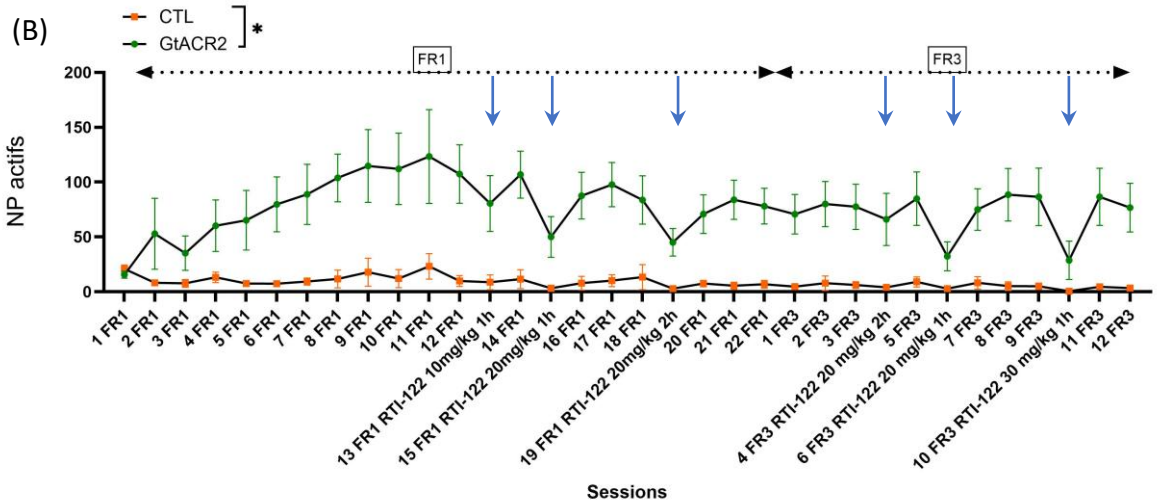
Comportements de type addictif ± RTI-122

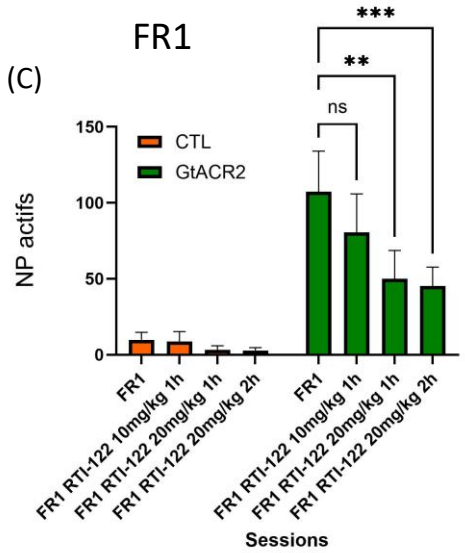
↓ : RTI-122 (i.p.)

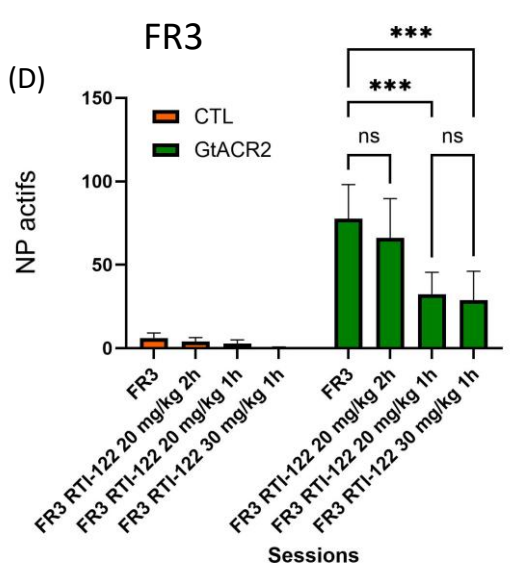
NP : Nosepoke

Acquisition





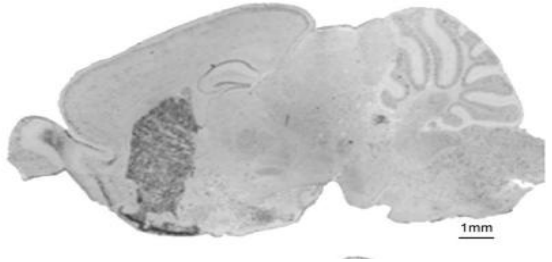




RTI-122 ↘ Opto-inhibition neurones MOR-VTA
⇨ ↘ **Recherche de récompenses**

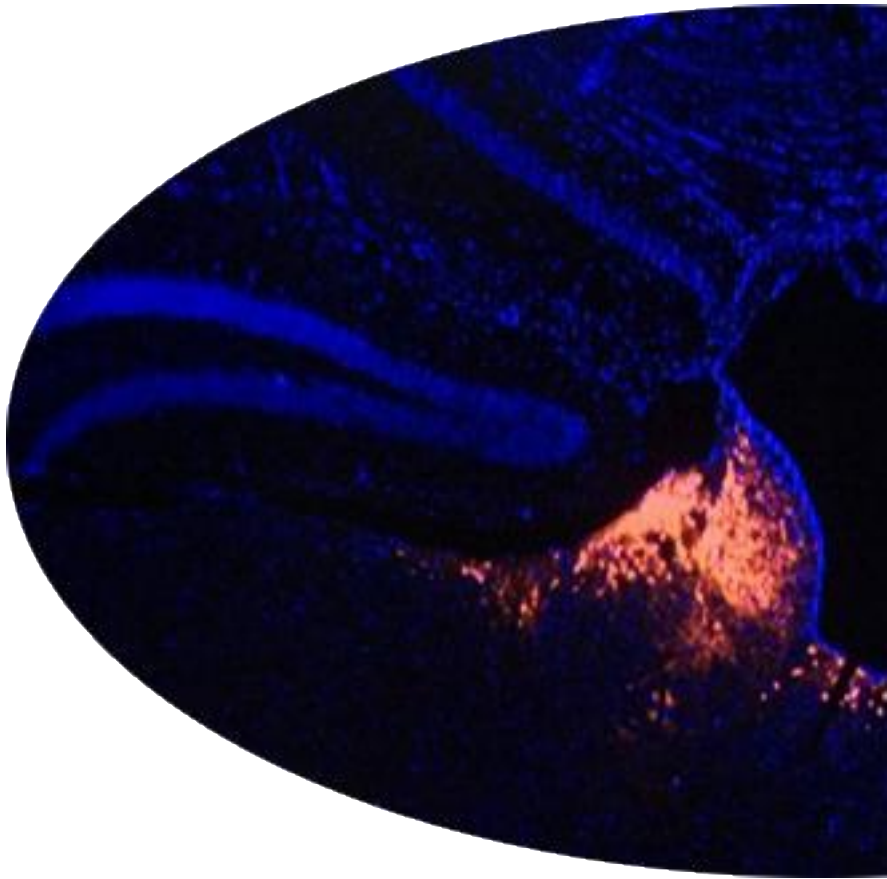
*(A, B, C, D) Test d'ANOVA à 2 facteurs à mesures répétées (A : p = 0,0102 ; B : p = 0,0147 ; C : p = 0,02 ; D : p = 0,04), test de comparaisons multiples de Tukey post-hoc. n = 6-8/groupe. Significativité statistique * : p < 0,05 ; ** : p < 0,01 ; *** : p < 0,001. Moyenne ± S.E.M.*

- **GPR88 et striatum**



Réduit la consommation d’alcool et la préférence aux opiacés

GPR139 et Habénula



Habenula and depression in human

CORRESPONDENCE

Remission of Major Depression Under Deep Brain Stimulation of the Lateral Habenula in a Therapy-Refractory Patient

Medical Hypotheses (2007) 69, 1305–1308

ELSEVIER

medical hypotheses

http://intl.elsevierhealth.com/journals/mehy

Deep brain stimulation of the lateral habenula in treatment resistant major depression ☆

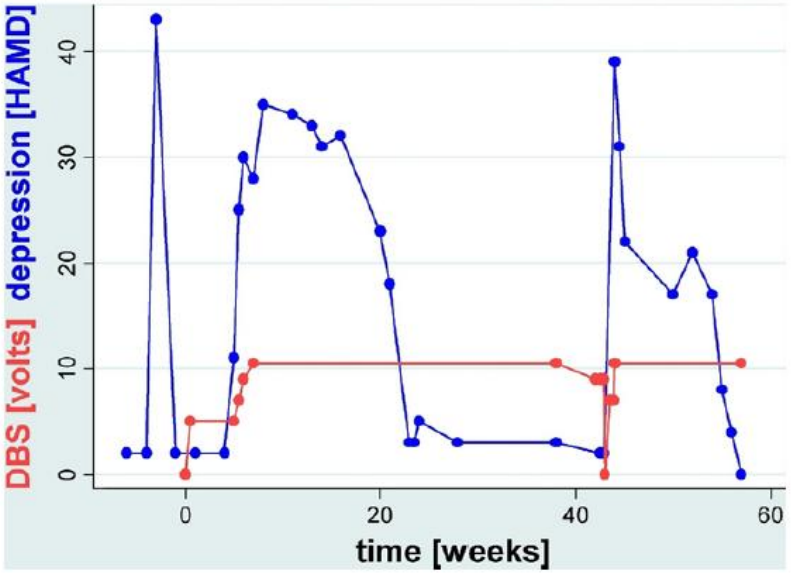
Alexander Sartorius [a,*], Fritz A. Henn [a,b]

[a] Central Institute of Mental Health, J5, D-68159 Mannheim, Germany
[b] Brookhaven National Laboratory, Life Sciences Directorate, Upton, NY, USA

Received 22 March 2007; accepted 23 March 2007

OPEN ACCESS

EMBO Molecular Medicine



Sartorius et al, 2010 Biological Psychiatry

A new translational target for deep brain stimulation to treat depression

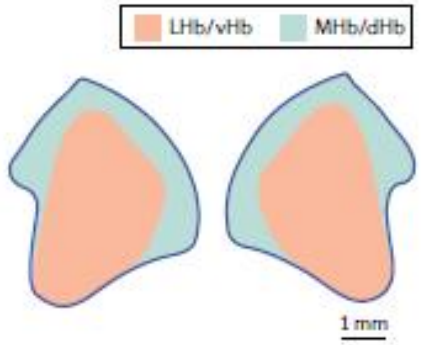
Karl Kiening[1], Alexander Sartorius[2]*

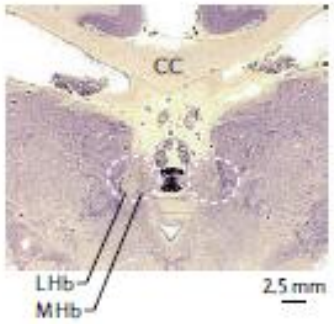
Keywords: DBS; depression; lateral habenula; Learned Helplessness; treatment resistance
DOI 10.1002/emmm.201302947

- Habenula is a new target to treat major depression

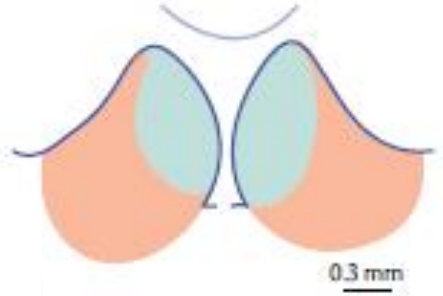
Habenula across species

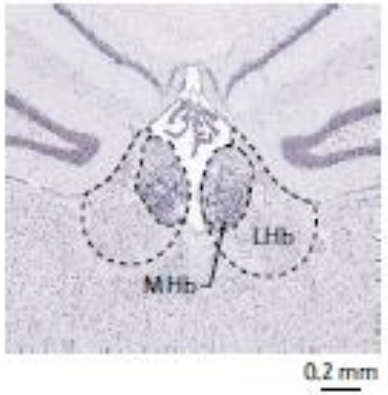
Human



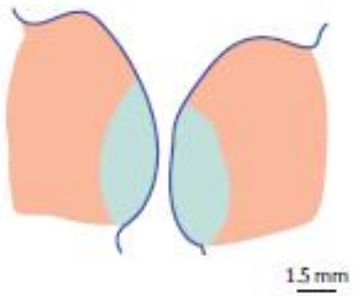


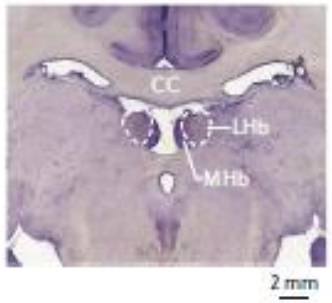
Mouse



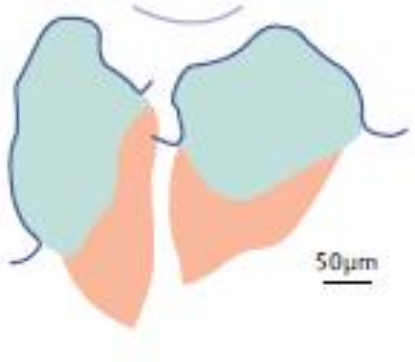


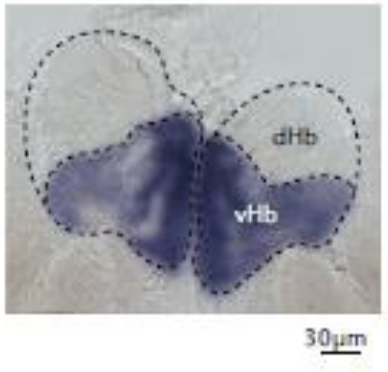
Rhesus monkey





Zebrafish





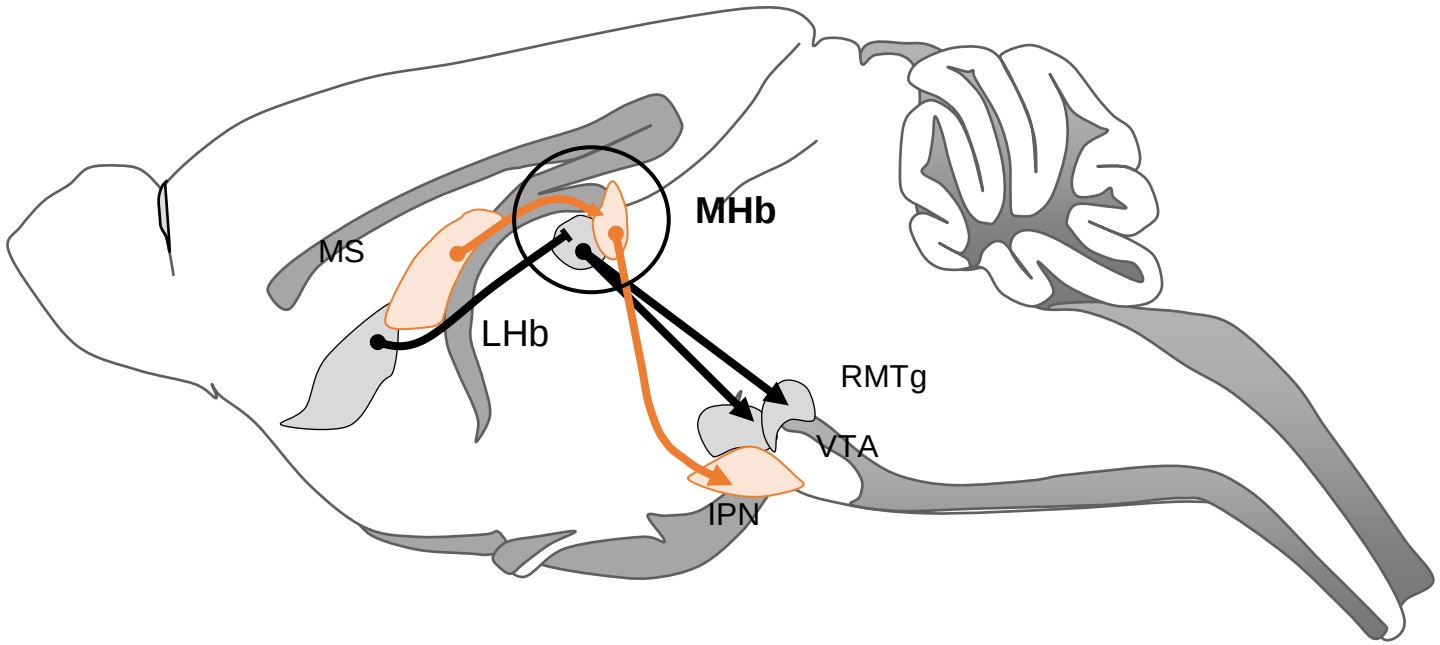
Adapted from Hu, Cui and Yang 2020 Nature Reviews Neuroscience

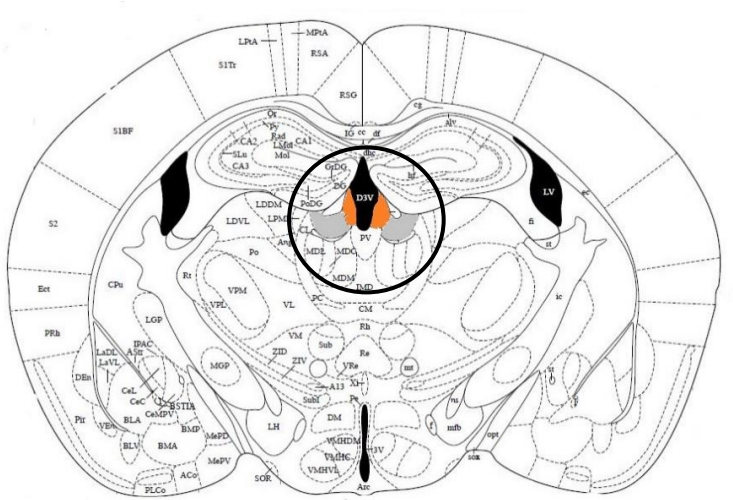
► Habenula is a highly conserved epithalamic structure

Habenula

Habenular Circuitry in Rodents

Boulos, Darcq and Kieffer 2017 Biological Psychiatry





Functions

- Reward/aversion Proulx et al, 2014 Nat Neuroscience
- Decision making Namboodiri et al, 2016 Current Biology
- Mood states/ Depression/ Addiction Lee et al, 2019 Frontiers in Psychiatry; Mathis and Kenny 2019 Neurosci Biobehav Rev; Ables et al. 2023 Pharmacological Research

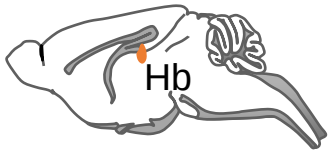
Habenula and aversion: GluN3A

NEUROSCIENCE

Control of aversion by glycine-gated GluN1/GluN3A NMDA receptors in the adult medial habenula

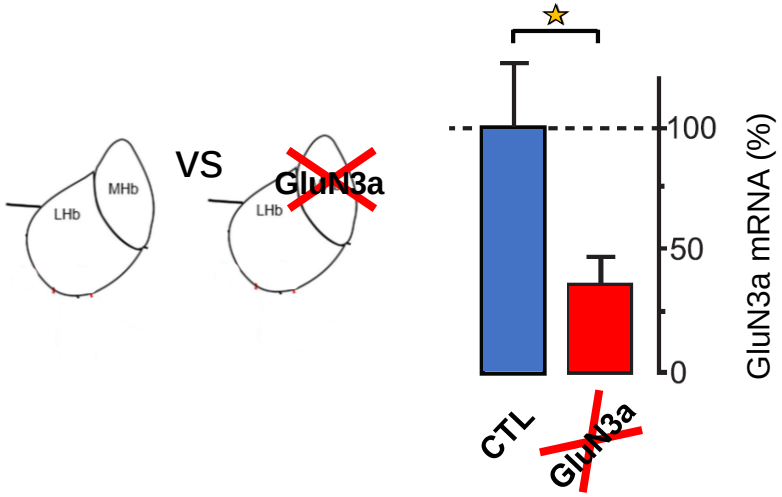
Y. Otsu[1]*†, E. Darcq[2]†, K. Pietrajtis[3]†, F. Mátyás[4,5,6], E. Schwartz[3], T. Bessaih[3], S. Abi Gerges[3], C. V. Rousseau[1]‡, T. Grand[1], S. Dieudonné[1], P. Paoletti[1], L. Acsády[4], C. Agulhon[7], B. L. Kieffer[2], M. A. Diana[3]§

Science 2019

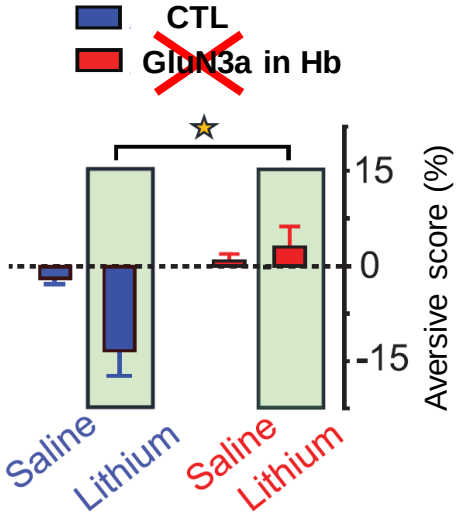


M. Diana

Reduction of GluN3a expression in habenula

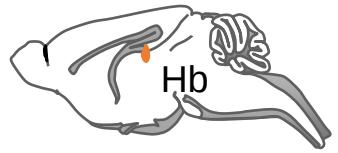


Decrease of lithium aversion



► Habenular GluN3A is required for the expression of aversive states

Habenula and aversion: MOR



Mu Opioid Receptor (MOR)

- Analgesia
- Euphoria

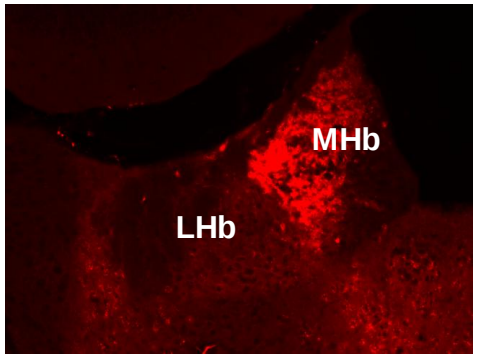
Neuropsychopharmacology

ARTICLE

Mu opioid receptors in the medial habenula contribute to naloxone aversion

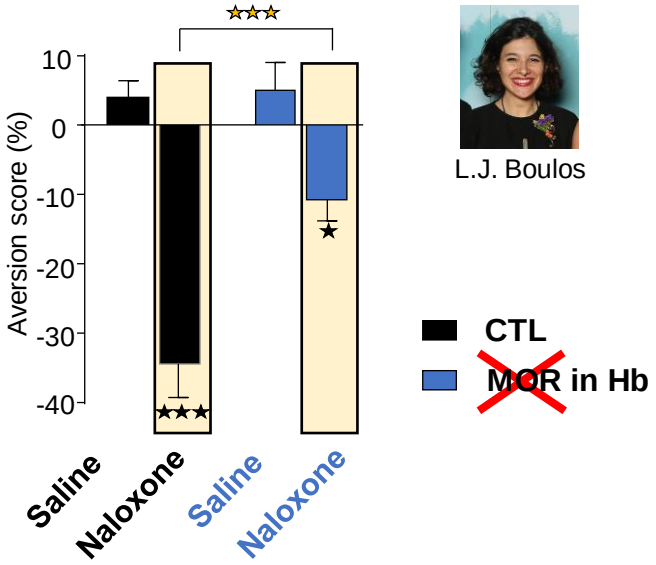
L. J. Boulos[1,2,3,4,5], S. Ben Hamida[1,2,3,4,5], J. Bailly[1], M. Maitra[1], A. T. Ehrlich[1,2,3,4,5], C. Gavériaux-Ruff[2,3,4,5], E. Darcq[1] and B. L. Kieffer[1,2,3,4,5] **2020**

MOR is enriched in habenula



Gardon et al., (2014) Neuroscience.

Reduction of Naloxone aversion

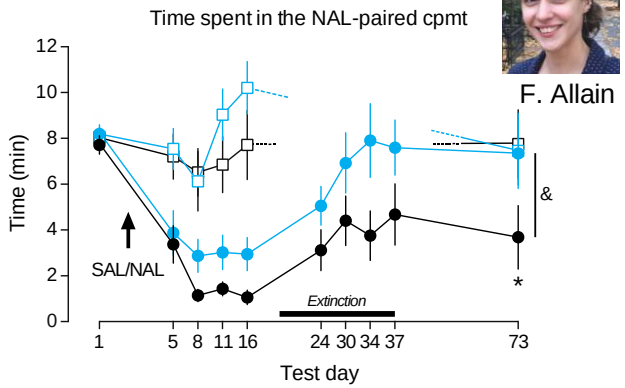


L.J. Boulos

CTL

~~MOR in Hb~~

F. Allain

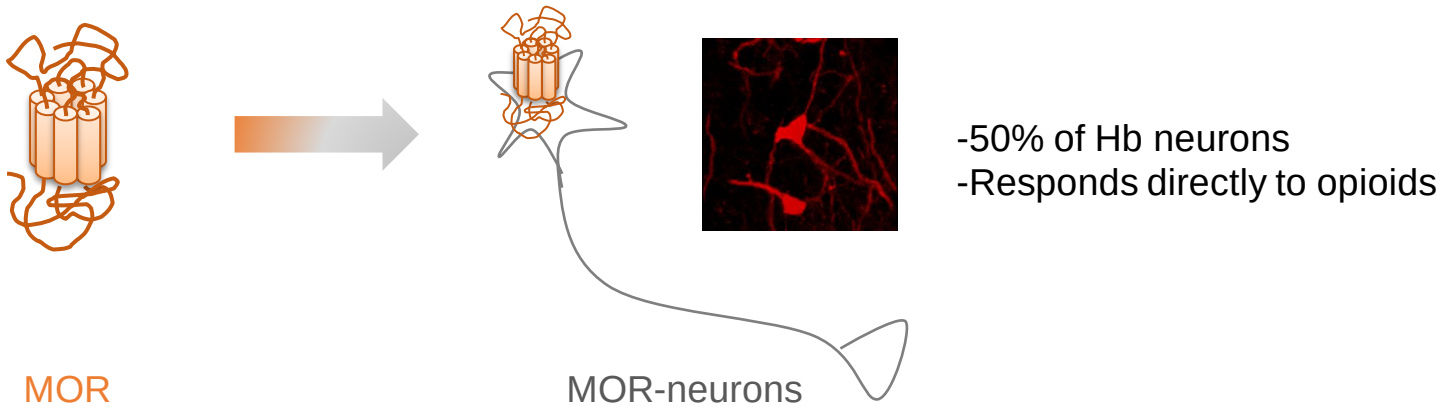


Bailly et al, Biological Psychiatry 2023

► MOR in Hb modulate the expression of aversive states

Question

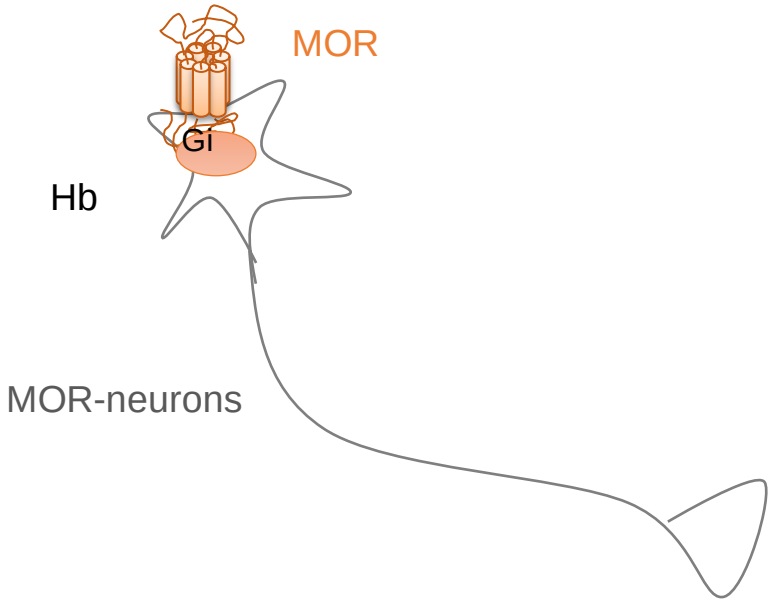
What are the roles of Hb MOR-neurons?



-50% of Hb neurons
-Responds directly to opioids

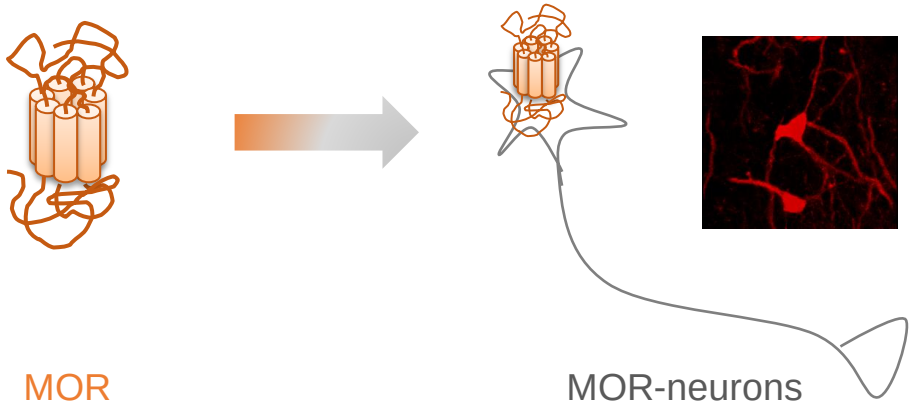
Hypothesis:

► **Hb MOR-neurons mediate aversive states**



Question

What are the roles of Hb MOR-neurons?



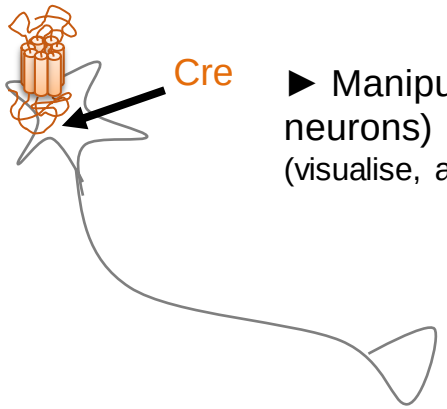
-50% of Hb neurons
-Responds directly to opioids

Hypothesis:

►Hb MOR-neurons mediate aversive states

New genetic tool

KI mouse
MOR promotor-Cre Recombinase



► Manipulation of neurons sensitive to opioids (MOR-neurons)
(visualise, activate/inhibit)

Bailly et al, 2020 eNeuro

► Focus on the role of Hb MOR-neurons

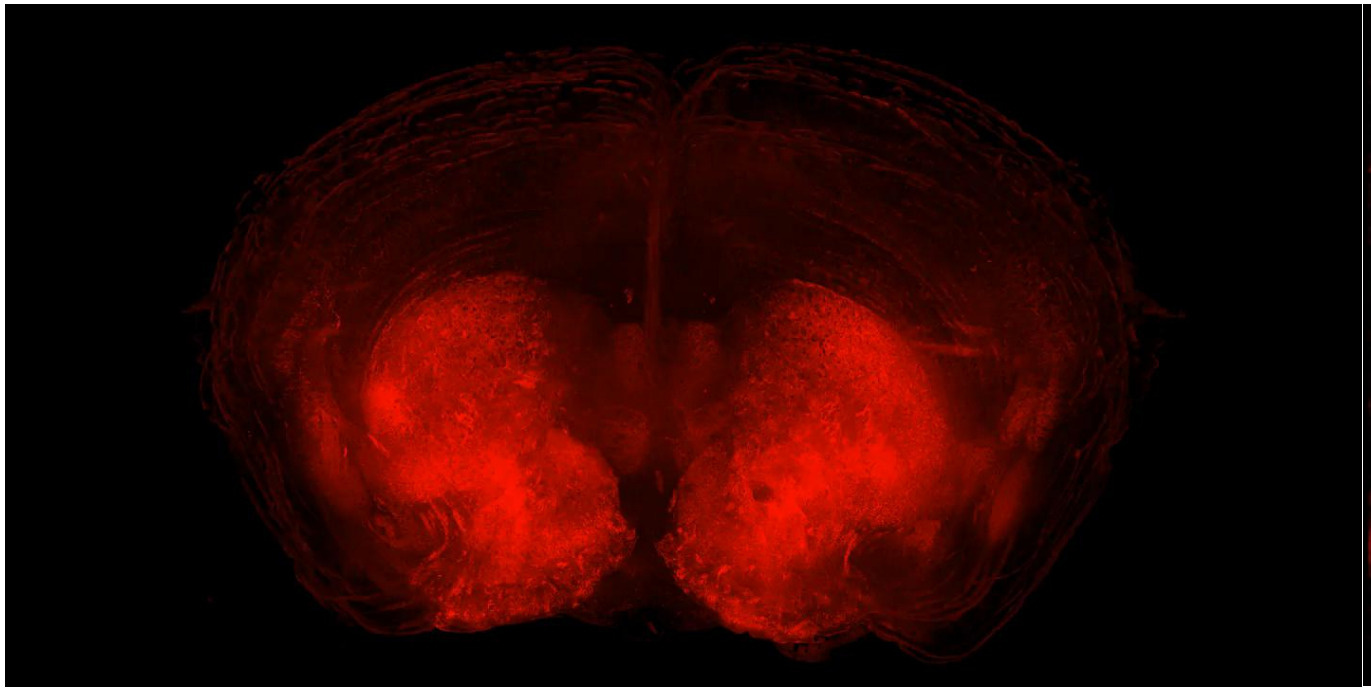
Tool to characterize MOR-neurons

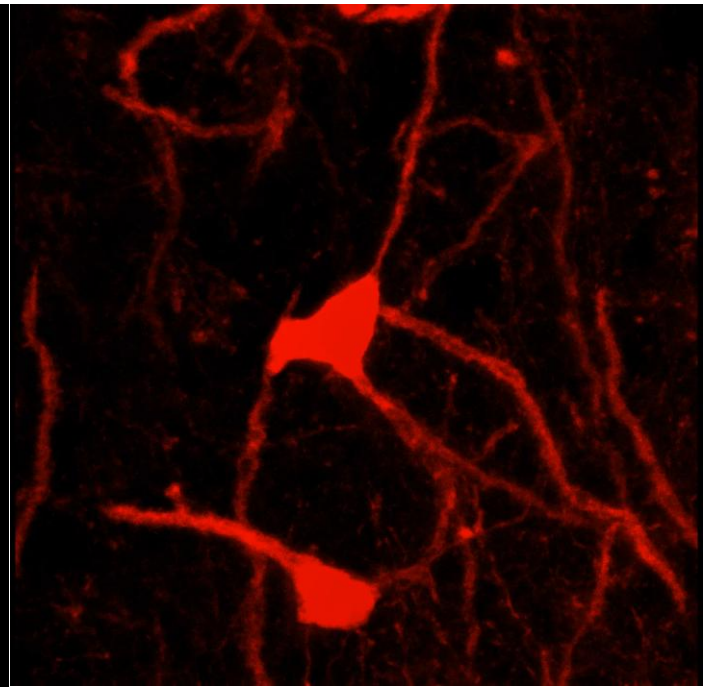
MOR-Cre Mice

Julie Bailly
PhD, McGill

Charles Dupuy
Master, UNISTRA

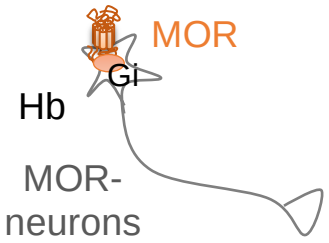
MOR-neurons in adult brain

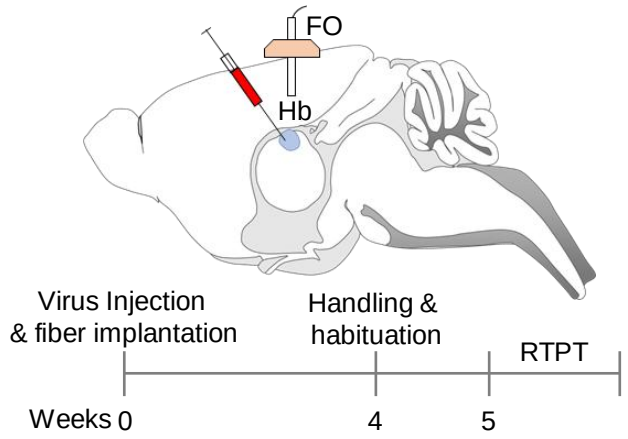


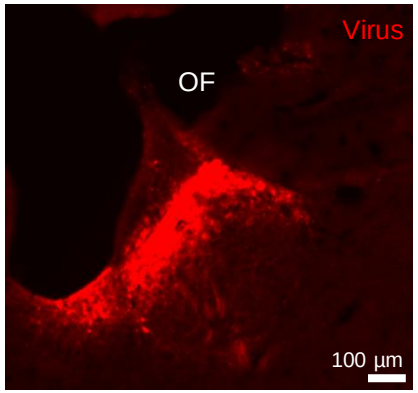


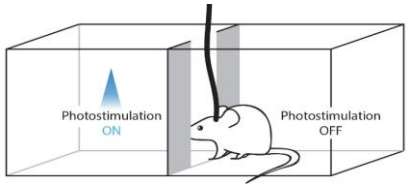
Bailly et al, 2020 eNeuro

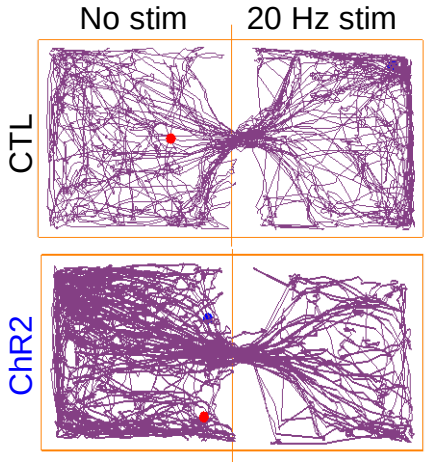
Role of Hb-MOR neurons



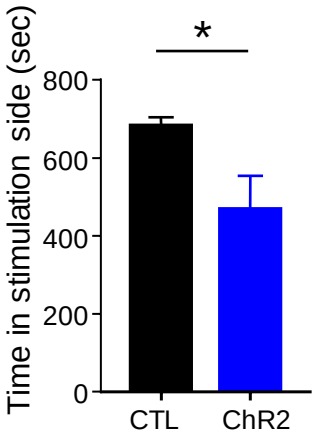








Avoidance (Real time place testing)



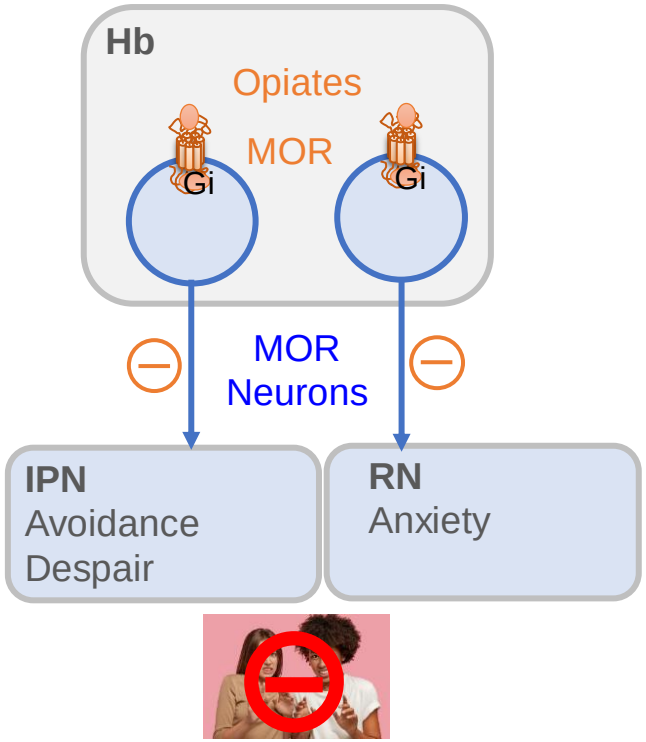
► Hb-MOR neurons encode aversive states

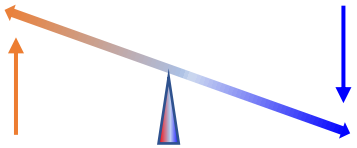
Julie Bailly

Bailly et al, Biological Psychiatry 2023

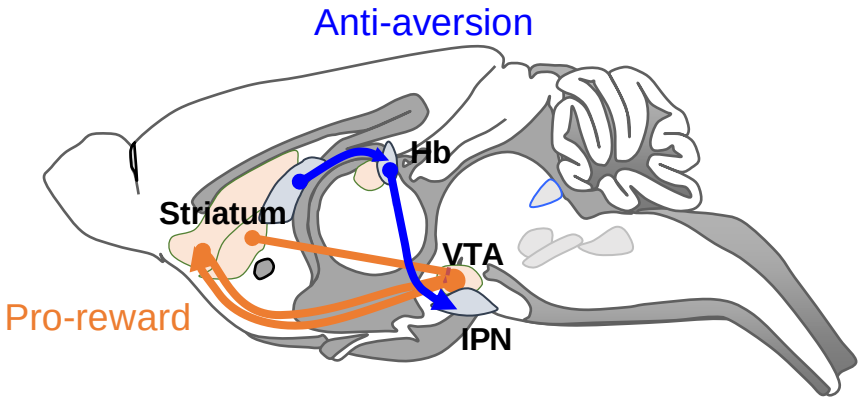
Basal states: HB-MOR neurons and behavior

Opioids may limit aversive states by inhibiting Hb MOR-neurons
– an “anti-aversion” role –





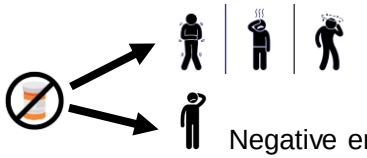
Hedonic Balance



► Do dysfunctions in Hb MOR-circuitry contribute to the development of a negative affect (drug withdrawal and abstinence / mood disorders)

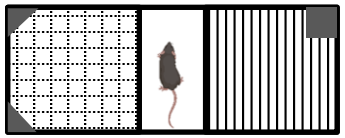
Perspectives

Hb-MOR - Negative emotional state in withdrawal ?



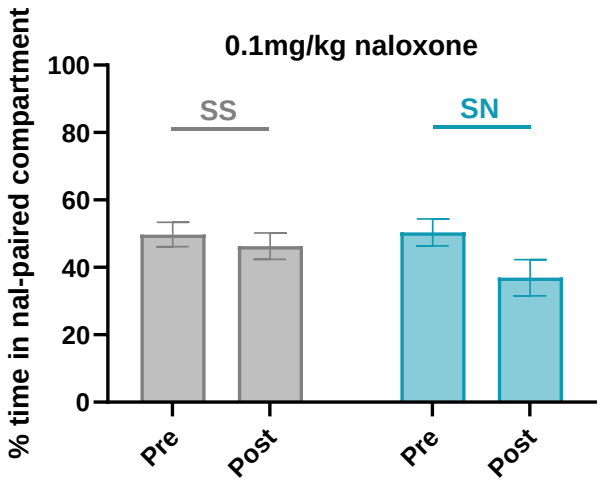
Negative emotions?

Dersu Ozdemir

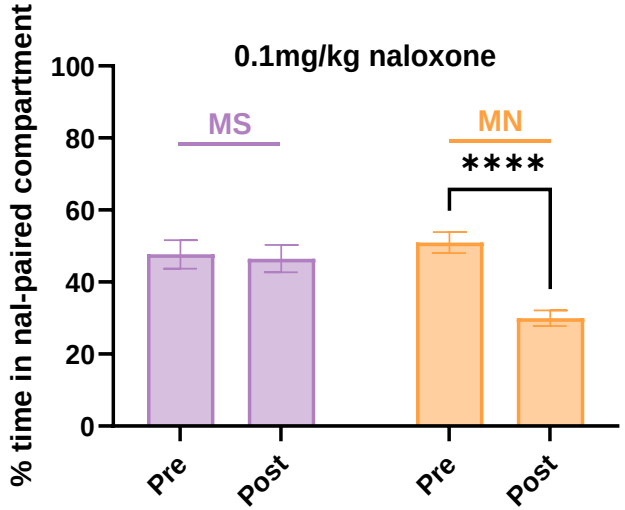


Place aversion to naloxone (0,1 mg/kg)
in naïve and dependent animals

Naive



Opioid- dependent



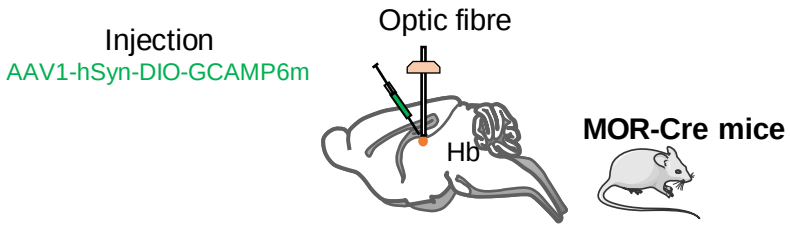
Unpublished; n=10-13

► **Naloxone aversive effect is stronger in dependent that in naive animals**

Hb-MOR - Negative emotional state in withdrawal ?

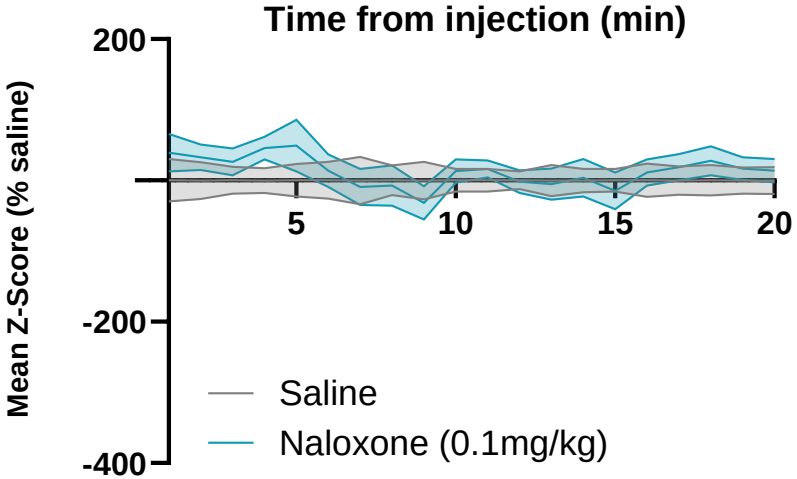
Dersu Ozdemir

Calcium activity of Hb-MOR by fiberphotometry

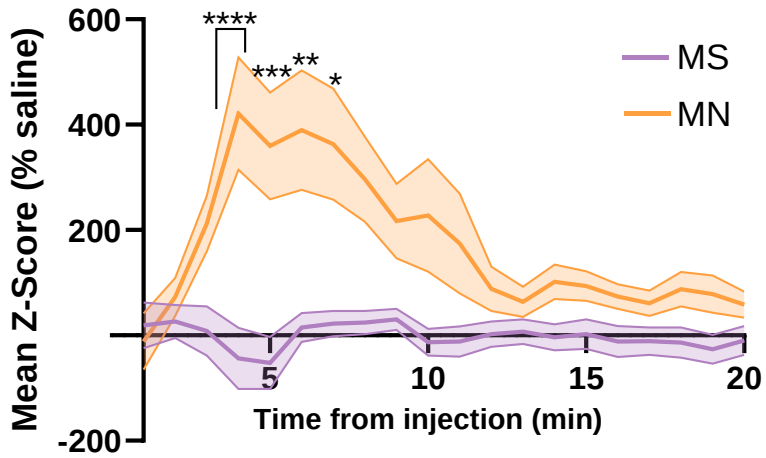


Hb-MOR response to acute naloxone (0.1 mg/kg)

Naive



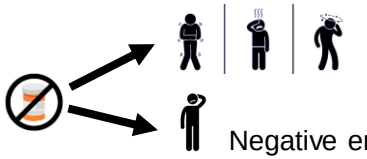
Opioid- dependent



► naloxone activity in Hb-MOR neurons is enhanced in dependent animals

Unpublished, n=10-18

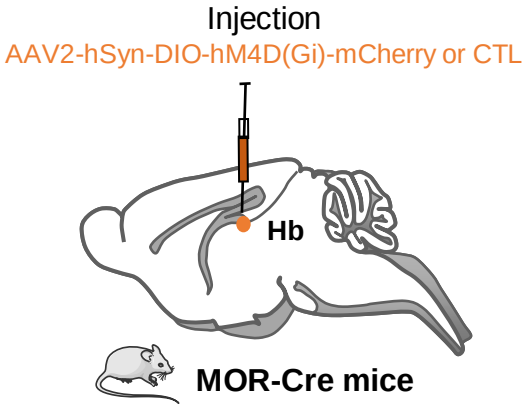
Hb-MOR - Negative emotional state in withdrawal ?

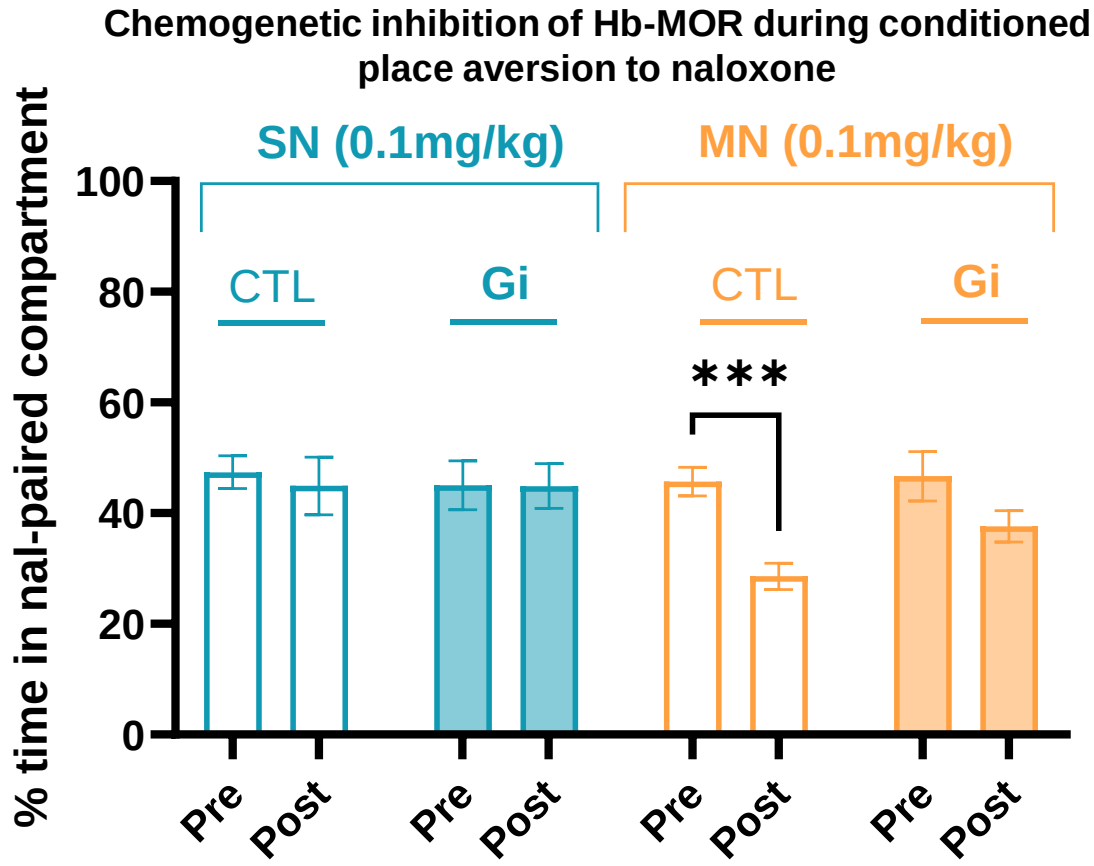


Dersu Ozdemir

Hypothesis

► **reducing Hb-MOR neuron activity during naloxone conditioning limits the development of avoidance**





► Inhibition of Hb-MOR neurons decreases naloxone-conditioned place aversion in morphine-dependent mice

Unpublished; n=10-16

► Dysfunctions in MOR-circuitry contribute to the development of a negative affect (drug withdrawal)

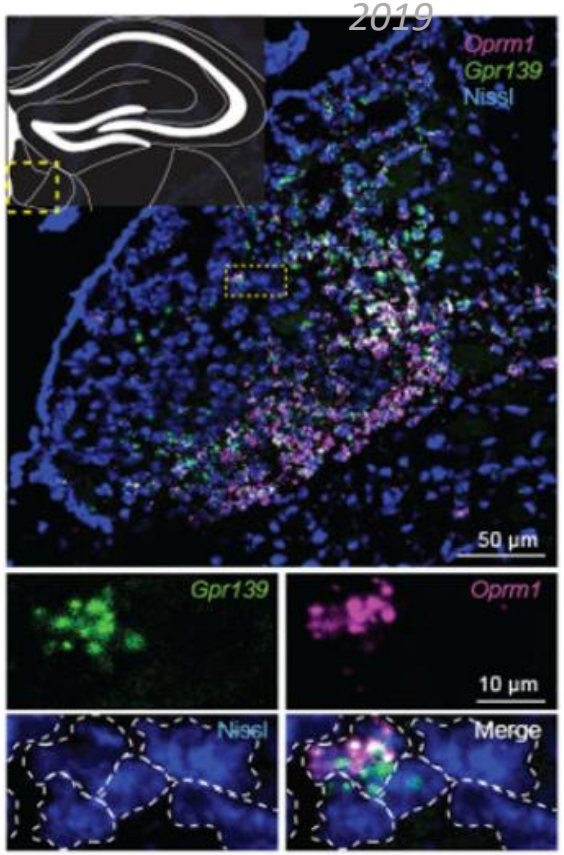
GPR139

- GPR139 enriched in Hb

Liu et al., 2015

- GPR139- anti-opioid system

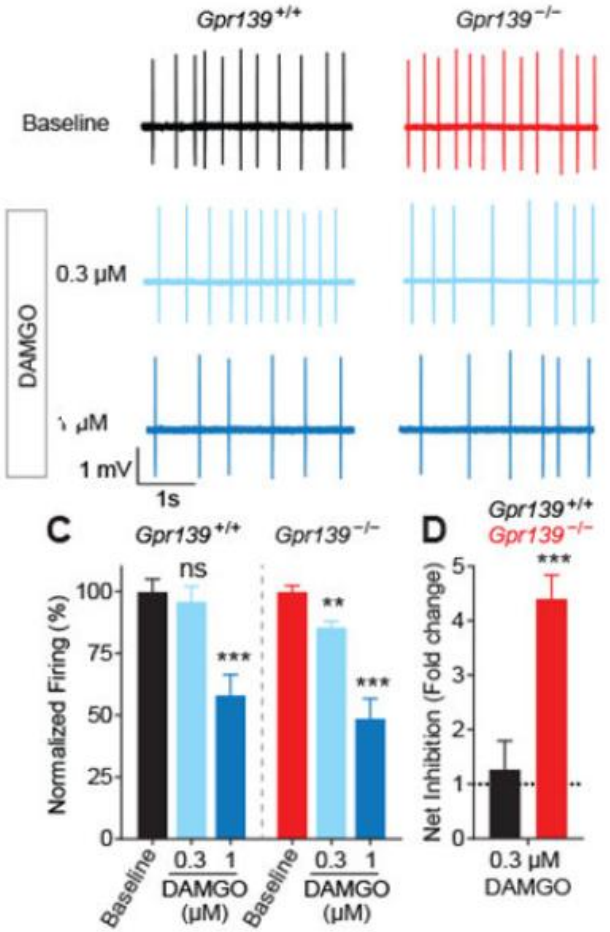
Wang et al., 2019



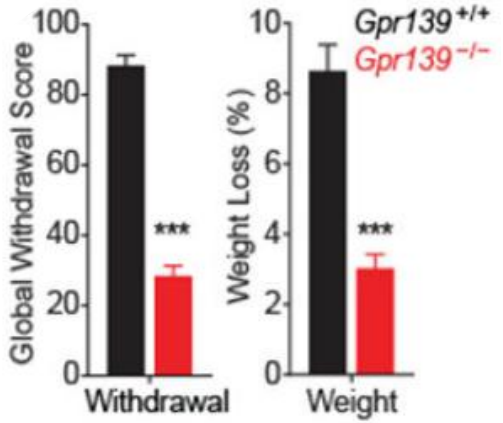
Wang et al., 2019

MOR and GPR139 co-expressed in Hb

GPR139 KO



GPR139 KO increased response to MOR agonist in Hb



GPR139 KO reduced **naloxone-precipitated somatic withdrawal signs**

GPR139 antagonism – treatment for opioid withdrawal?

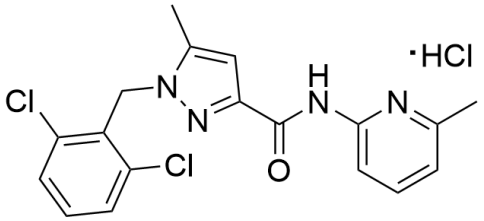
Dr. C Jin

Opioid-dependent

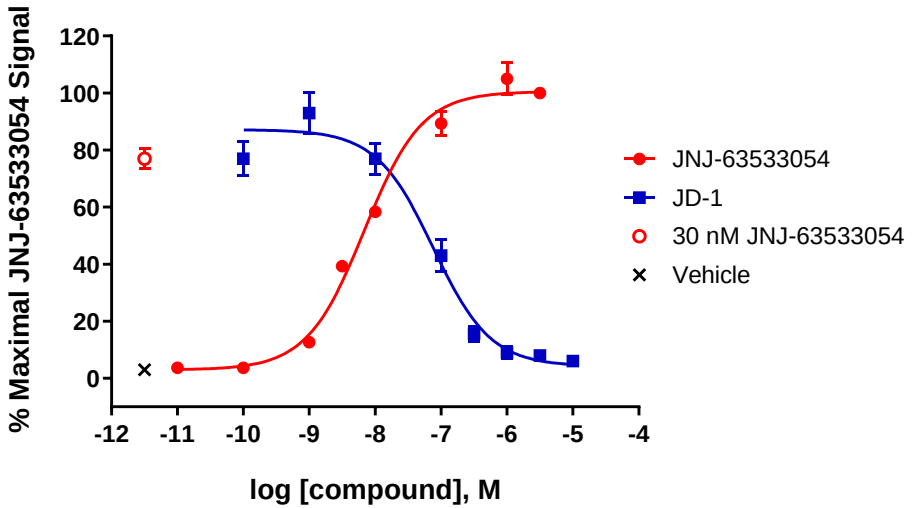
Hb-MOR neurons

GPR139 antagonist

Affective and somatic signs during opioid withdrawal



JD-1



IC50 curve of JD-1 Calcium mobilization assay

- Two-fold more **potent** than the known antagonist JNJ-3792165

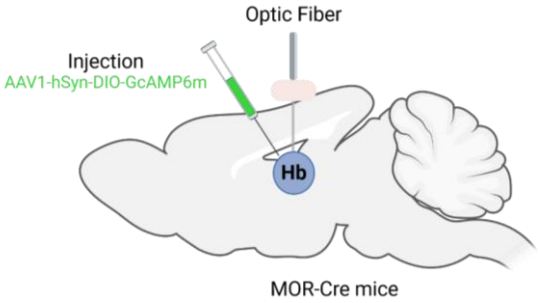
Nepomuceno et al., 2018

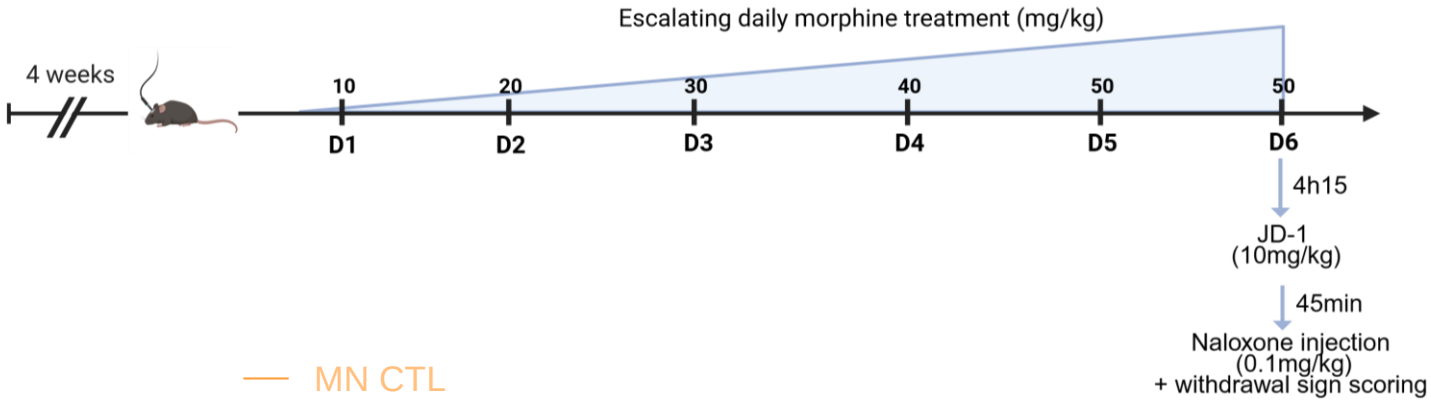
- **No agonist activity** at 10µM

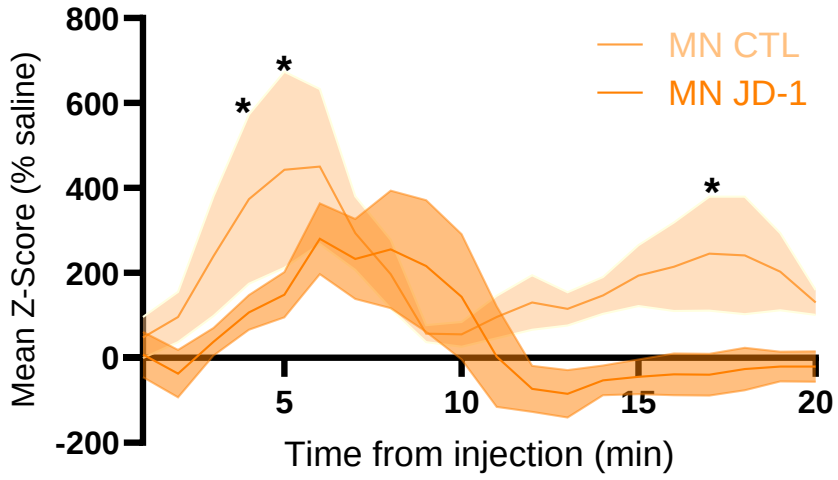
- **High selectivity:** <50% inhibition at 10 µM in radioligand binding assays of the NIMH Psychoactive Drug Screening Program (40 CNS targets)

JD-1 interaction with Hb-MOR neurons

Opioid-dependent

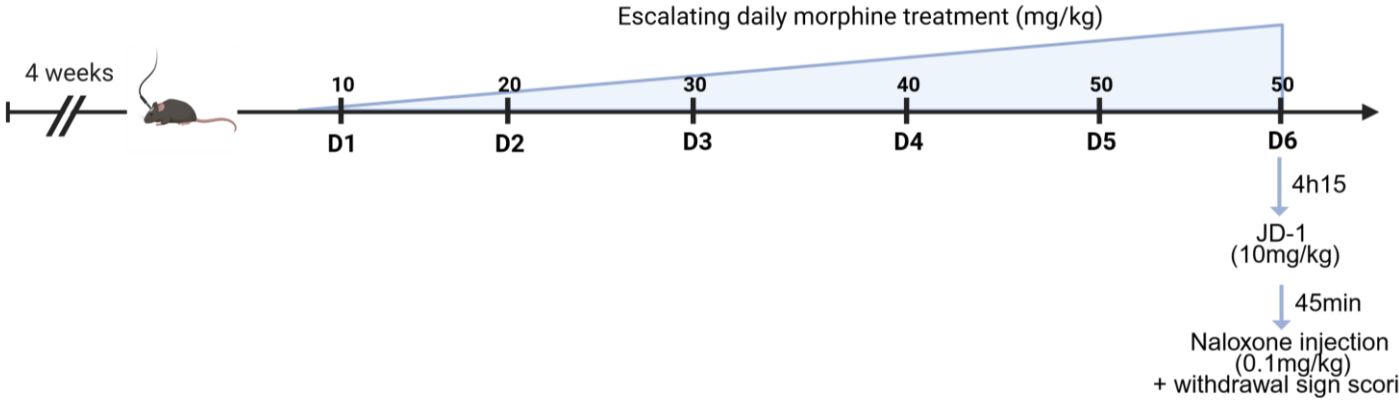


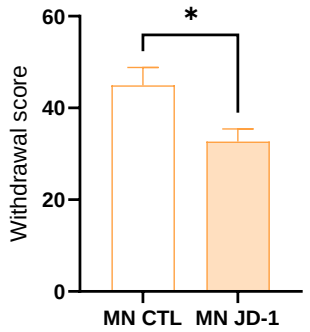


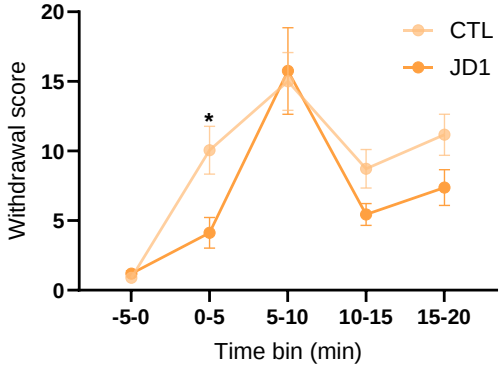


GPR139 antagonism reduced naloxone response in Hb-MOR neurons in an opioid-dependent state

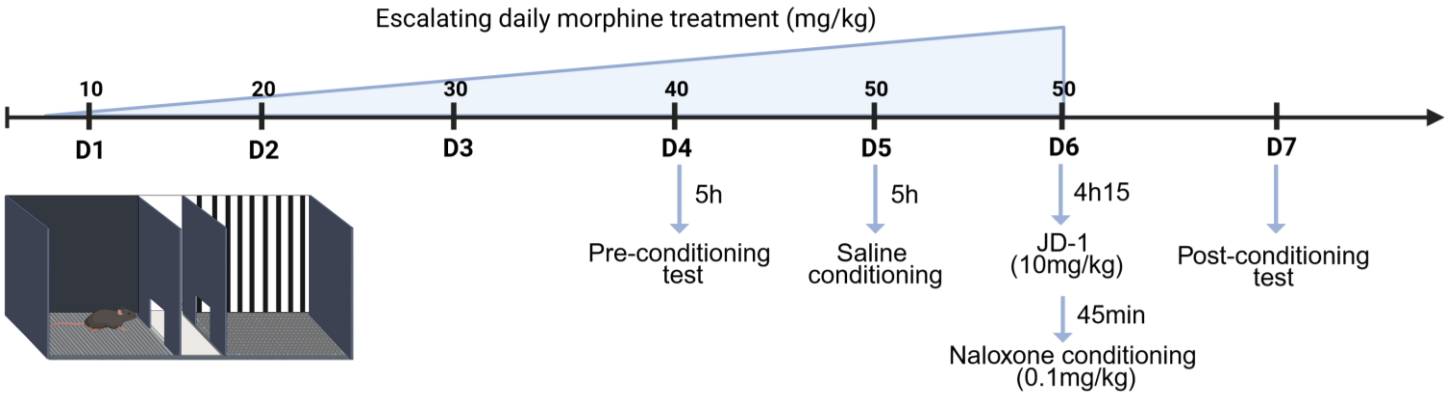
JD-1 reduces naloxone response

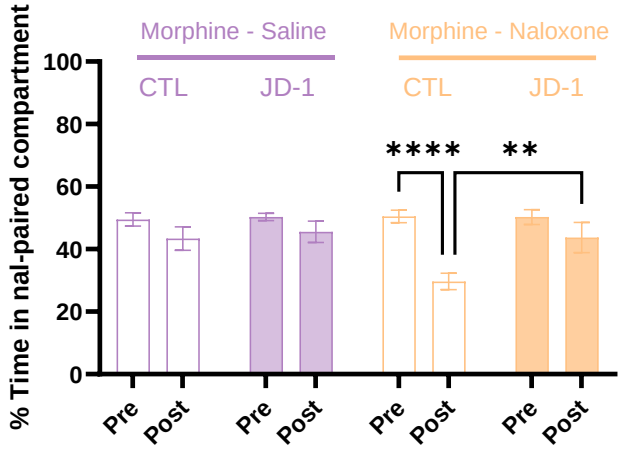






GPR139 antagonism reduced naloxone-induced somatic withdrawal signs

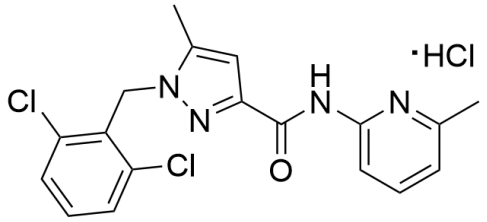




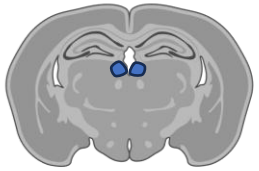
GPR139 antagonism reduced naloxone aversion

Conclusion

GPR139 antagonism:

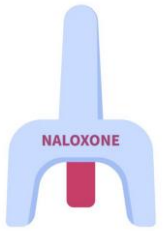


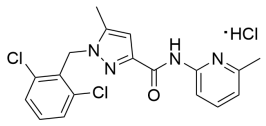
JD-1



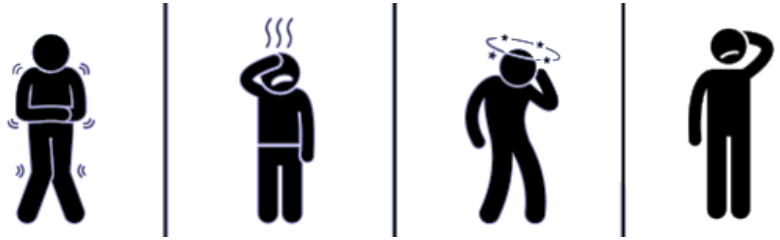
Reduced **Hb-MOR response to naloxone** after chronic morphine

Alleviated **somatic** and **aversive effects** of naloxone-precipitated morphine withdrawal

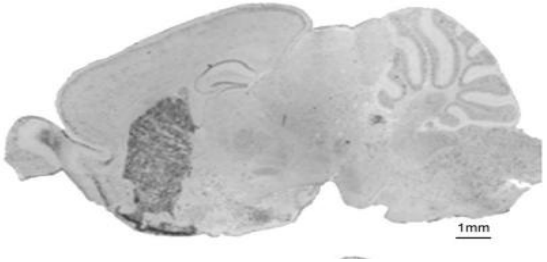




JD-1

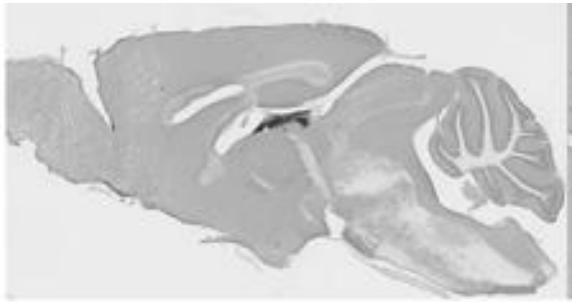


2 récepteurs RCPG orphelin



- **GPR88 et striatum**

Réduit la consommation d'alcool et la préférence aux opiacés



- **GPR139 et habénula**

Réduit les symptômes négatifs du sevrage aux opiacés

Thank you for your attention !

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Université de Strasbourg
Inserm

Donation

NIH National Institute on Drug Abuse

FRM Fondation Recherche Médicale

IReSP Institut pour la Recherche en Santé Publique

anr agence nationale de la recherche