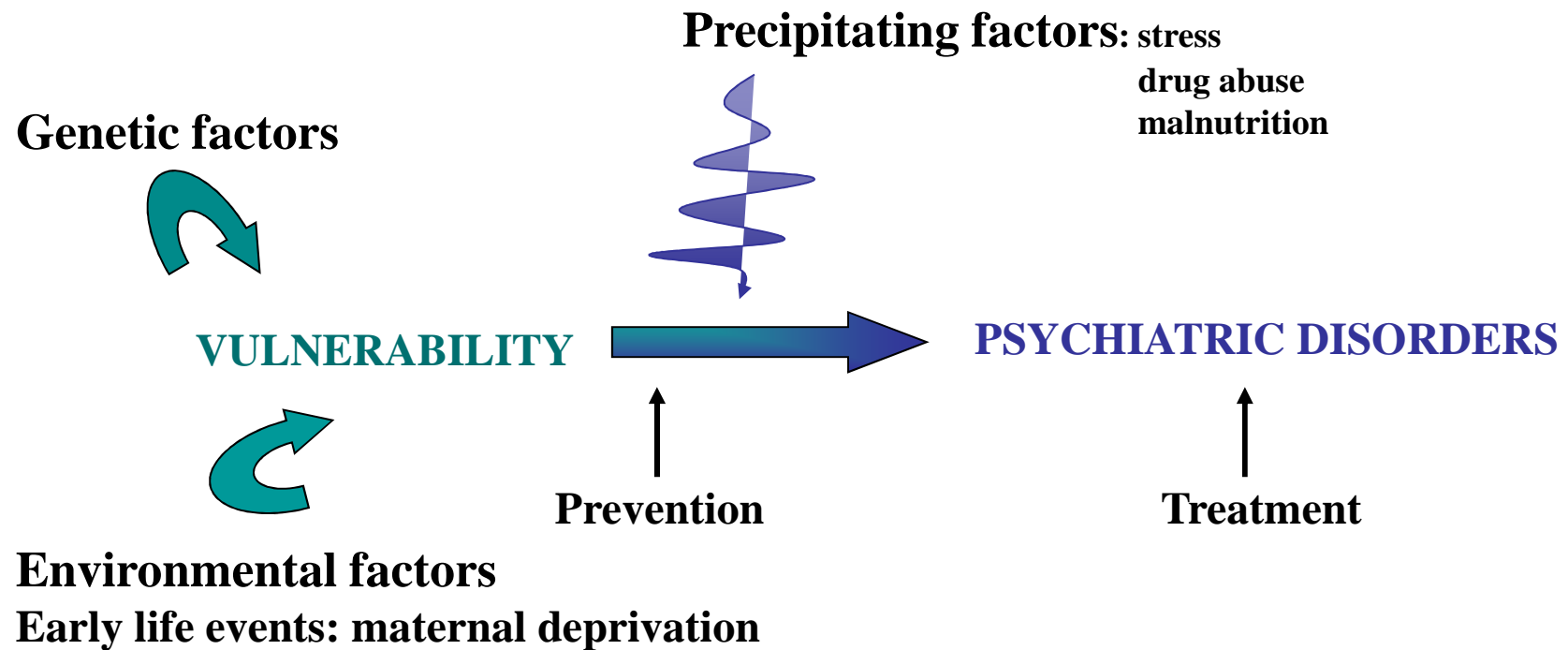


# Physiopathology and pharmacology of emotional disorders: Impact of the environment



Chez l'homme, des **perturbations relationnelles importantes entre la mère et le nouveau né** (longue séparation non compensée, manque de soins, affect négatif de la mère...) augmentent le **risque de survenue de pathologies graves: psychoses, troubles anxieux, syndromes dépressifs, conduites addictives** (Expertise collective INSERM 2002).

C'est l'importance fondamentale, dans toutes les espèces, des liens entre la mère et le nouveau né dans le développement harmonieux de ce dernier qui sous-tend la pertinence des modèles animaux de séparation mère/nouveau né.

La séparation constitue un **stress précoce, un manque de soins qui, parce qu'il survient pendant une période de développement neuronal intense**, est susceptible d'engendrer un fonctionnement cérébral anormal durable.

Intérêt: *décrire les conséquences neurobiologiques et comportementales néfastes  
contribuer à une meilleure prévention/prédiction des troubles mentaux  
améliorer nos stratégies thérapeutiques*

## LES MODELES

Séparation mère/nouveau-né

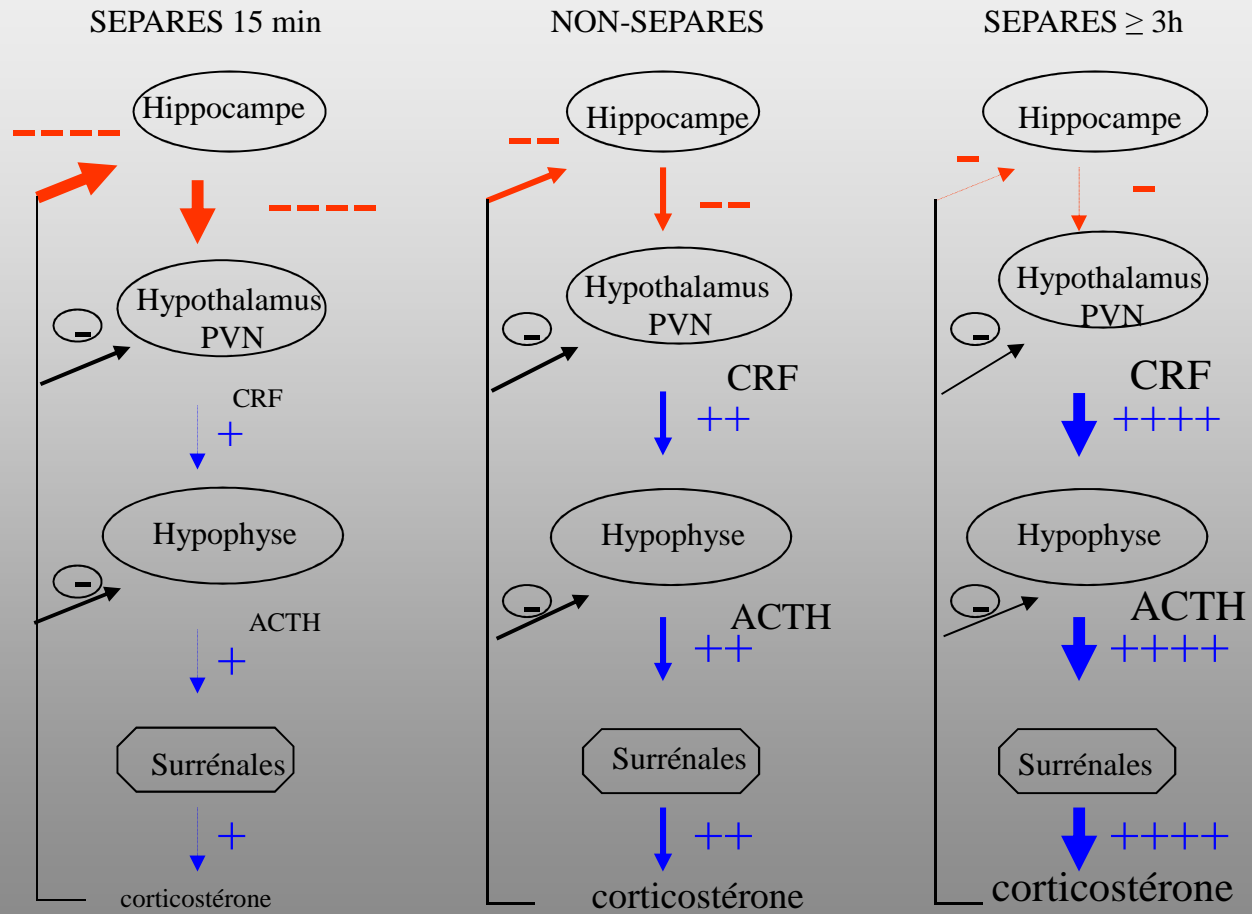
±stressante

- 15 min, 3h, 4h, 6h, 12h, 24h
- unique ou répétée
- ± précoce
- séparation mère et/ou des congénères

## IMPLICATION

- Manipulation humaine
- Altération du comportement maternel
- Isolement
  - environnement nouveau
  - manque de soins
  - manque de nourriture

# STRESS

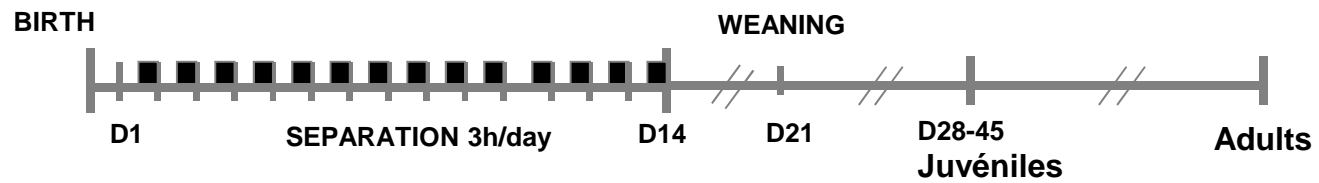


## MATERNAL DEPRIVATION MODEL

Long-Evans



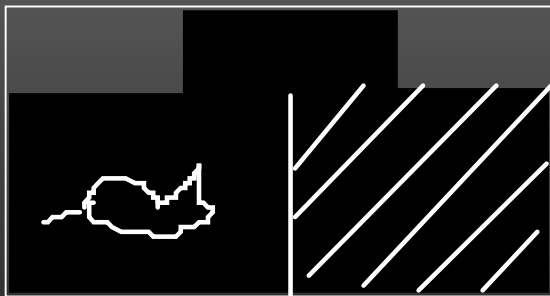
Mother and littermate separation



# DRUG DEPENDENCE



Place preference



Self-administration, IV, oral



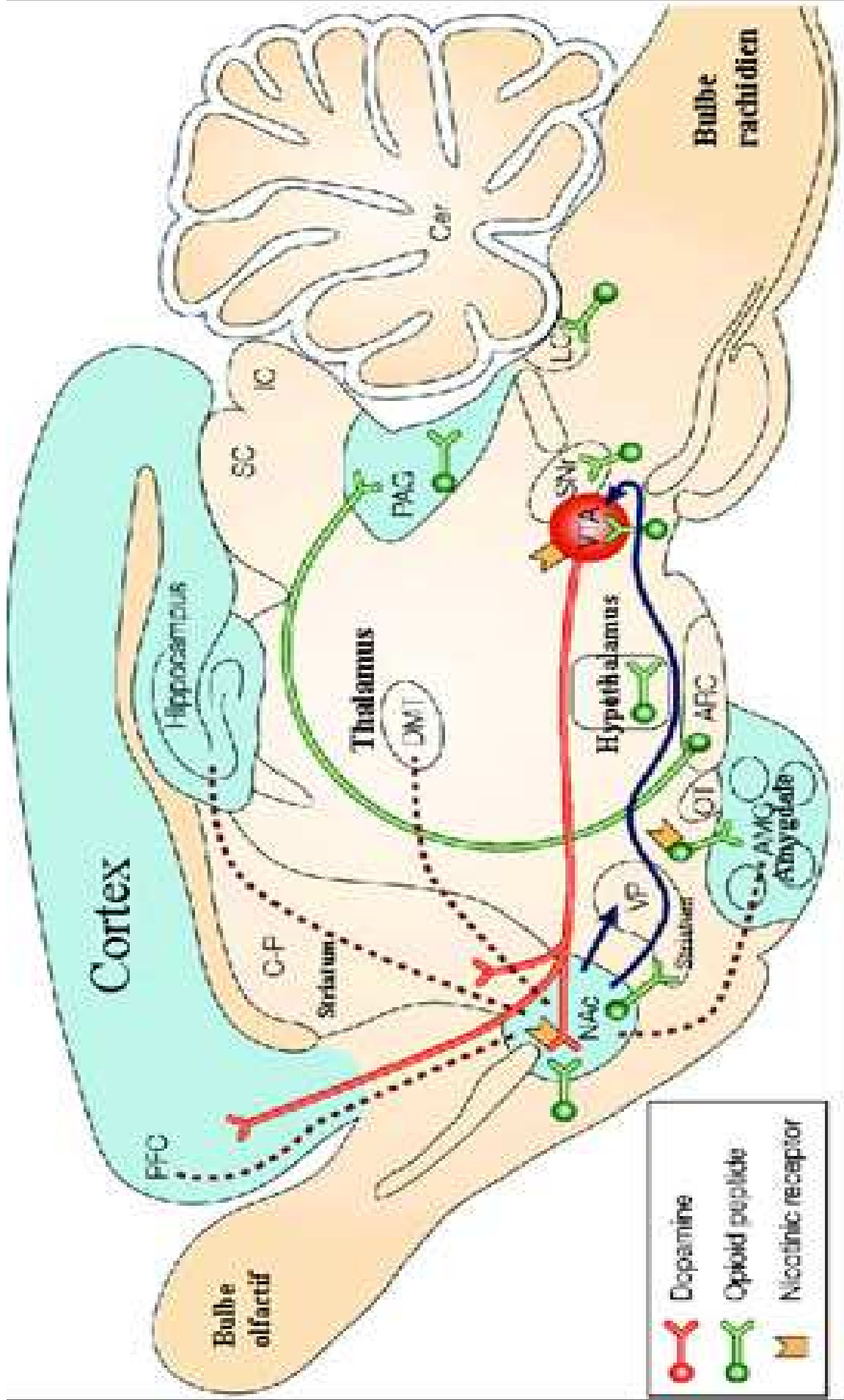
Thèses: Vincent Vazquez  
Lydie Morel

## Trois principaux systèmes de récompense

Dopamine

Endocannabinoïdes

Opiacés



→ Innervation du NAc sur l'ATV et le striatum

- - - Innervation du NAc par le cortex préfrontal, le système limbique et le thalamus



# OPIOIDES

## Préproenképhaline

Enképhalines  
Leu-, Met-ENK

$\delta, \mu$

Cortex  
Ganglions base  
Système limbique  
Hypothalamus  
SGP, NTS

Antinociception  
Euphorie-plaisir

## Préproopiomélanocortine

Endorphines( $\beta$ )  
Morphine

$\mu, \delta$

Cortex  
Ganglions base  
Système limbique  
Hypothalamus  
SGP, NTS

Antinociception  
Euphorie-plaisir

## Préprodynorphine

Dynorphines  
DYN A,B

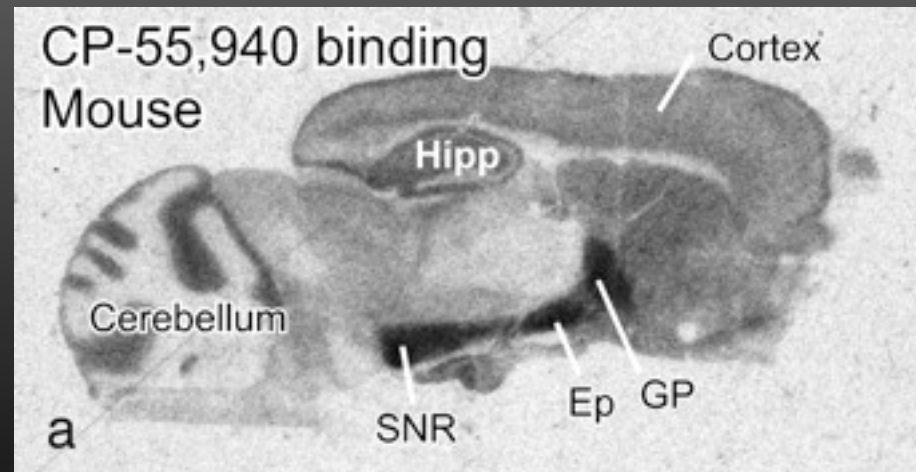
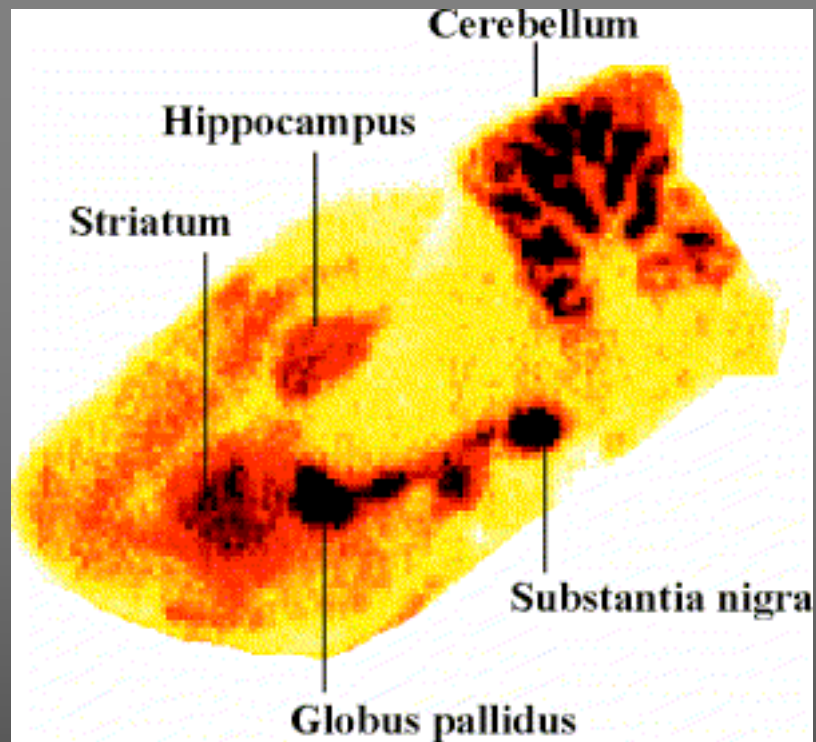
$k, \delta$

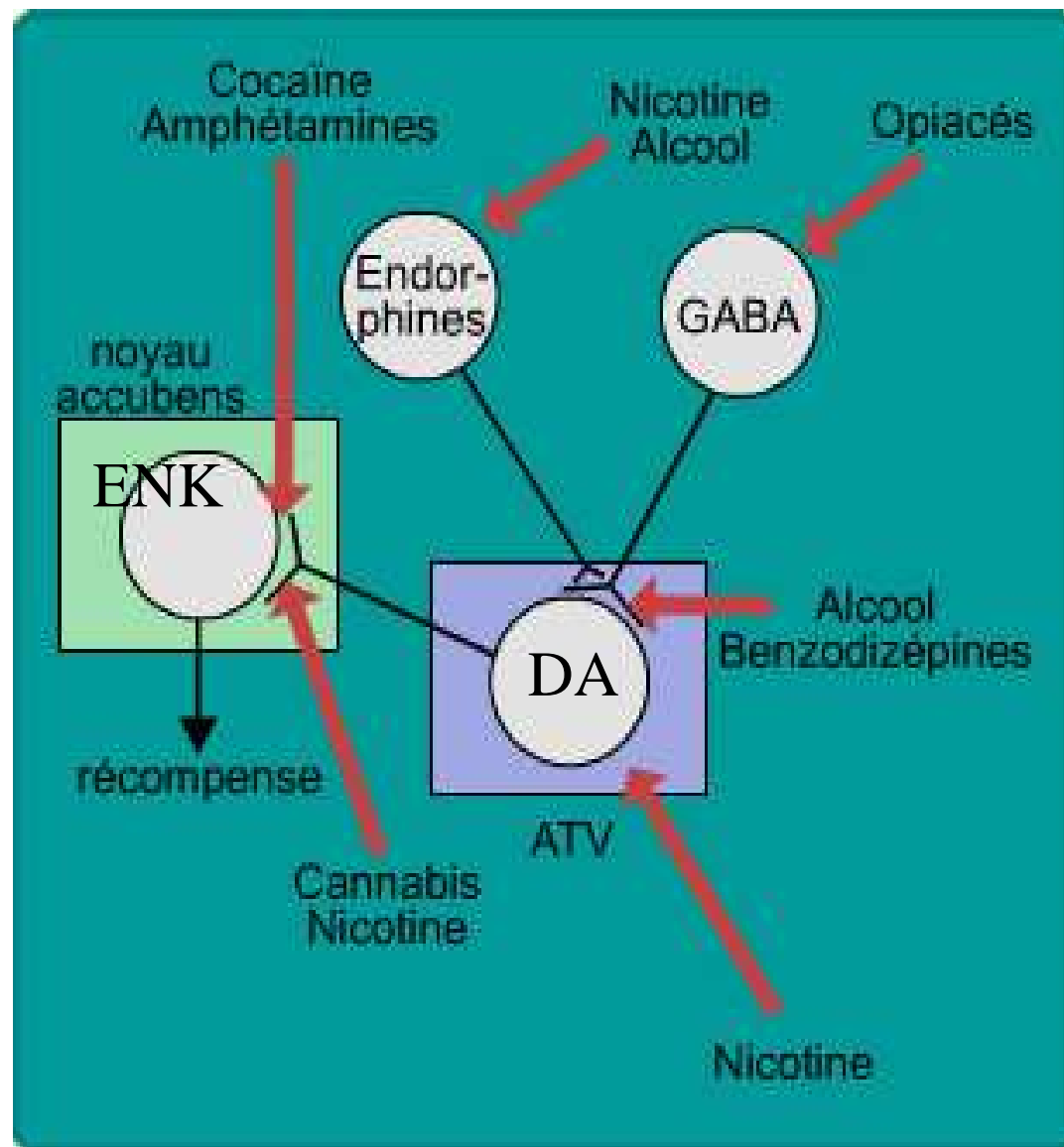
Système limbique  
Hypothalamus  
Hypophyse  
NTS

Antinociception  
Dysphorie  
Hallucination

Récepteurs CB1  
chez la souris

Anandamide  
Dérivés de l'acide  
arachidonique





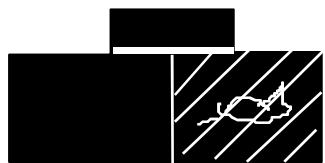
# MORPHINE PLACE PREFERENCE TEST: EXPRESSION-EXTINCTION



Pré-test



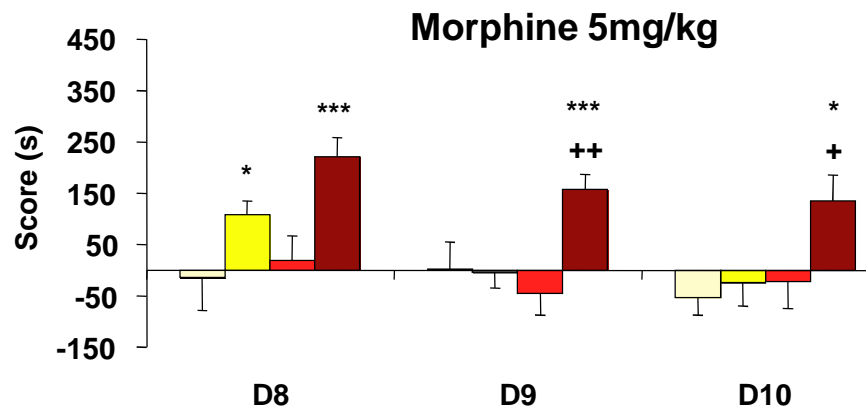
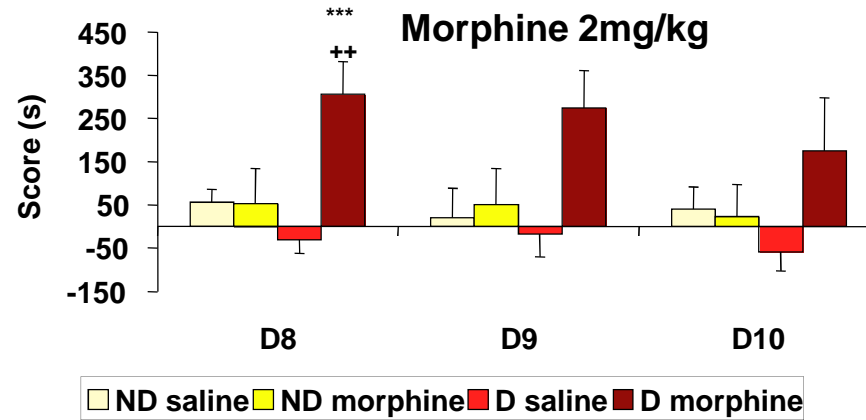
morphine



saline

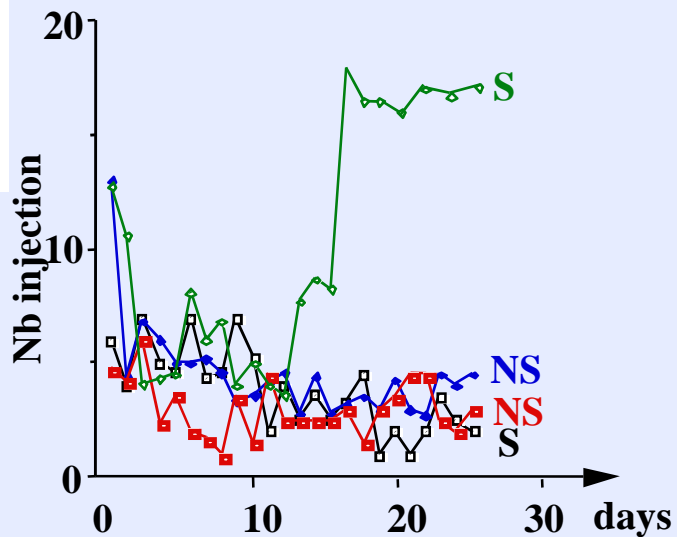
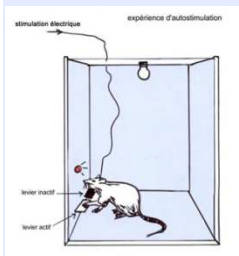


test

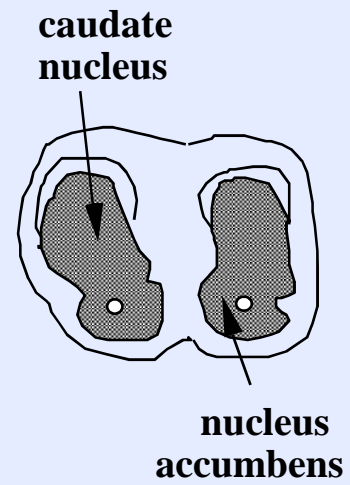
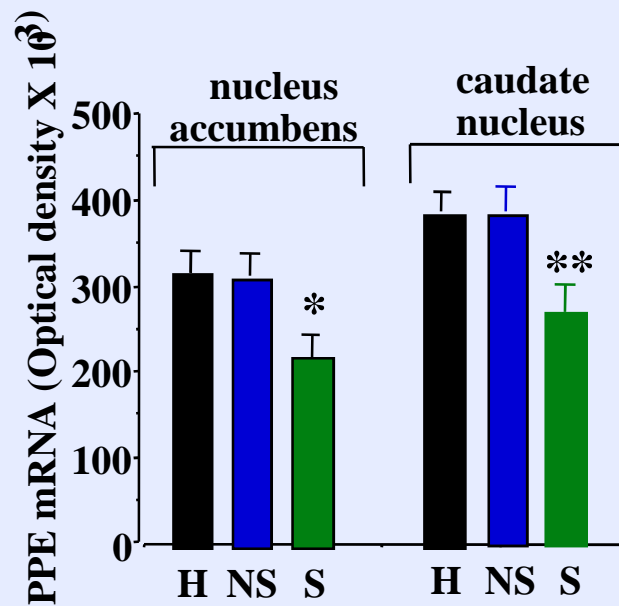


# IV Autoadministration

Héroïne 30 µg/kg/inj

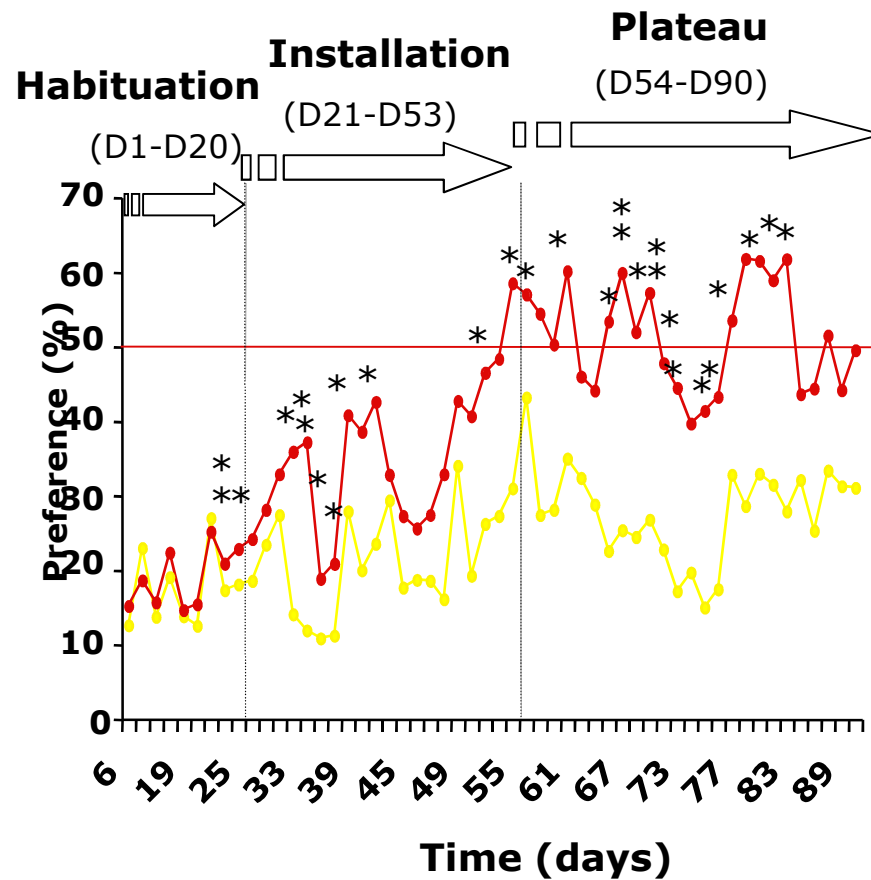


# PREPROENKEPHALIN mRNA

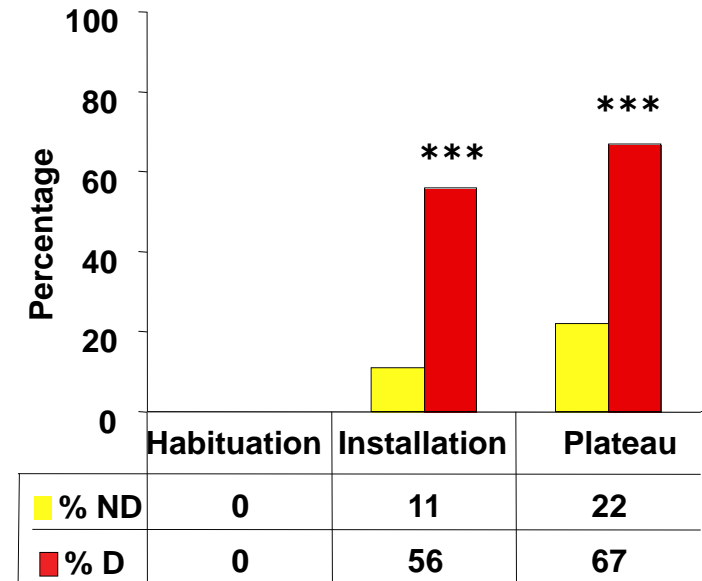


# Influence of maternal deprivation on morphine preference Oral self-administration

Morphine 25 mg/l

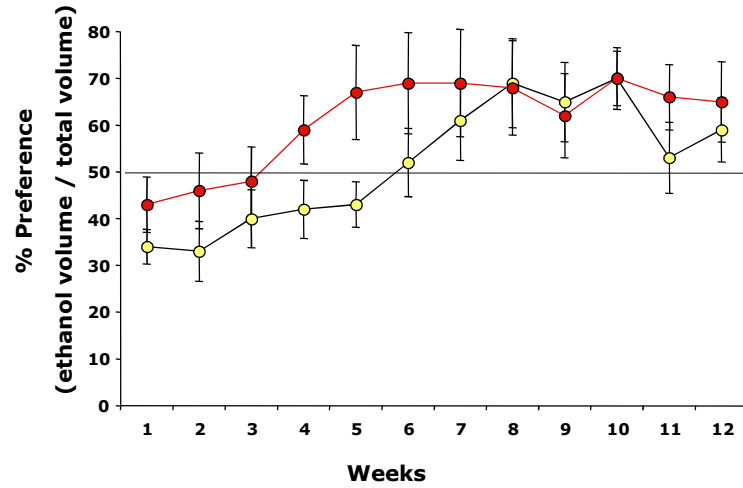


Percentage of rats showing  
>50% preference

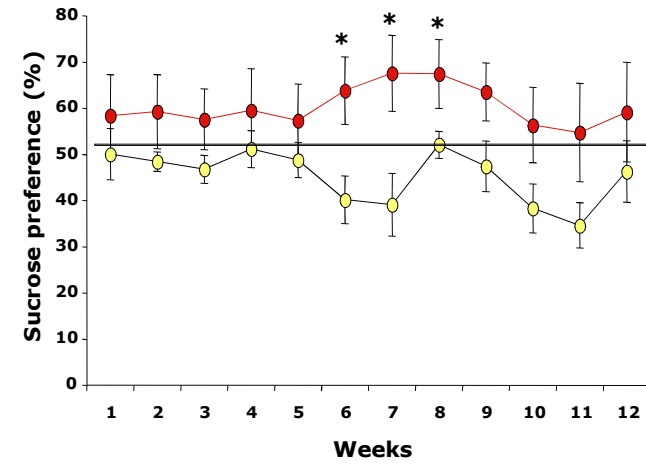


# ORAL SELF-ADMINISTRATION BEHAVIOR IN **NON-DEPRIVED** AND **DEPRIVED** RATS

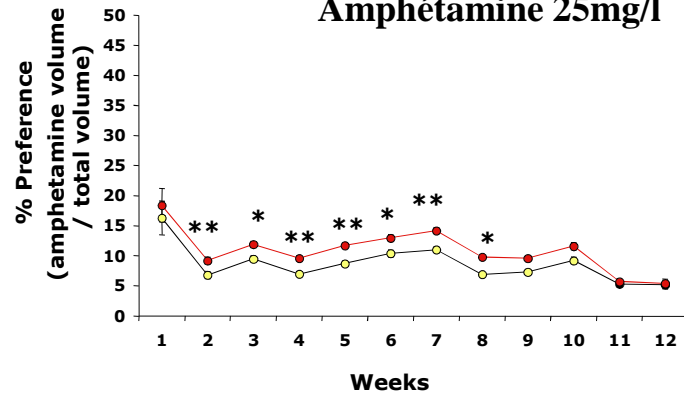
### Ethanol 10%



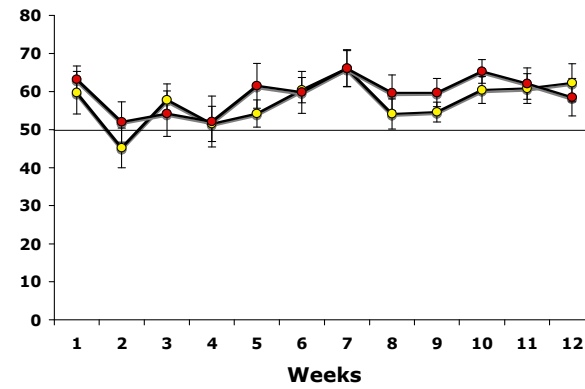
### Sucrose 0.025%



### Amphétamine 25mg/l

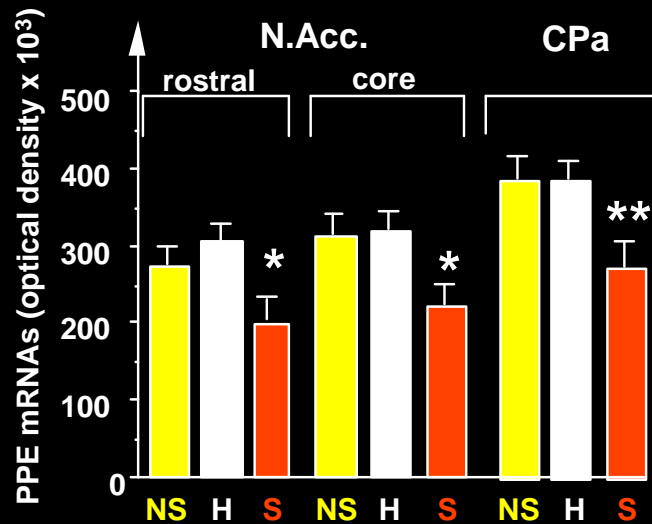


### Cocaïne 100mg/l

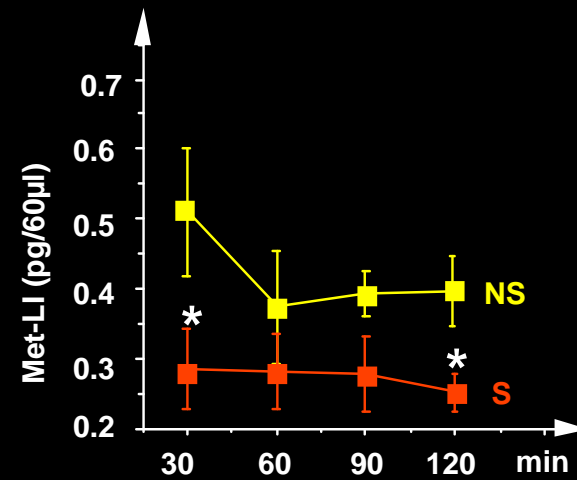


● D rat ● ND rat

**PPE mRNAs LEVELS IN THE NUCLEUS ACCUMBENS AND CAUDATE NUCLEUS OF NON-SEPARATED, HANDLED AND SEPARATED RATS**



**BASAL EXTRACELLULAR LEVELS OF MET-LI IN THE NUCLEUS ACCUMBENS OF NON-SEPARATED AND SEPARATED RATS**





**Maternal deprivation**

**hypersensitivity to the reward effect of morphine**

**morphine dependence**

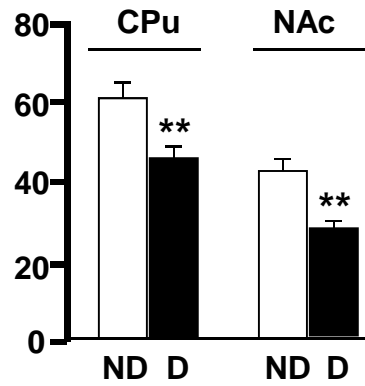
**hypoactivity of the enkephalinergic system**

**Why?**

**How to cure it?**

# WHY?

Preproenkephalin mRNA



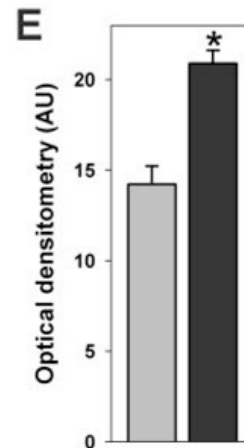
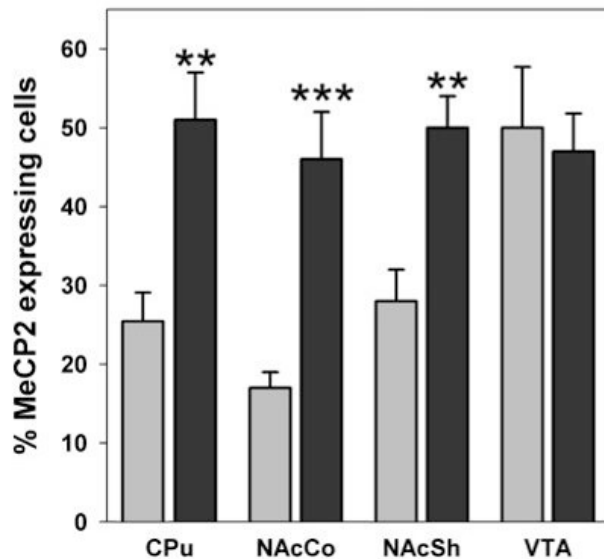
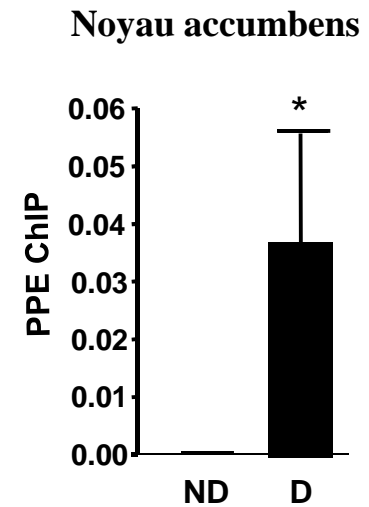
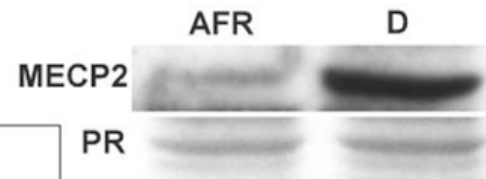
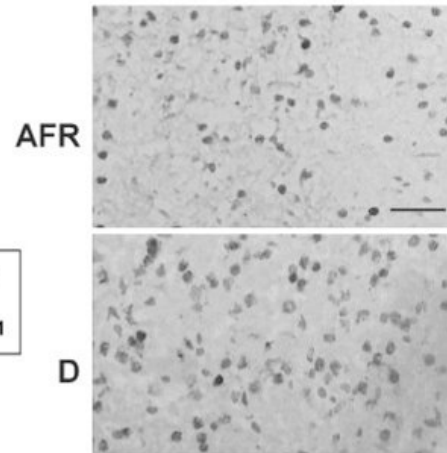
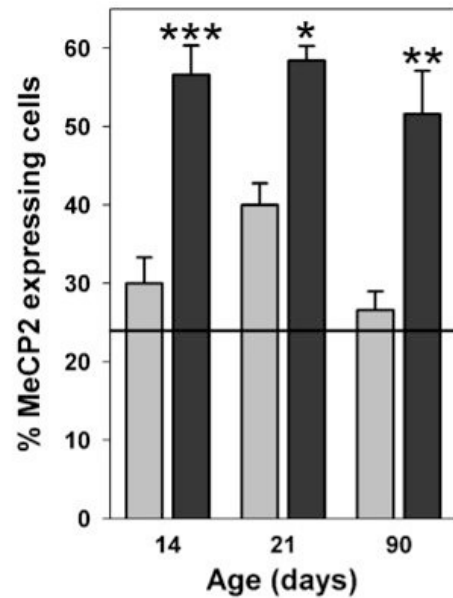
ND = AFR: control, D: deprived rats



**EPIGENETIC MECHANISMS MIGHT EXPLAIN VULNERABILITY TO OPIATE DEPENDENCE**

*collaboration: J. Zwiller-M. Meaney*

# Modèle de privation maternelle: methyl binding protein, MeCP2

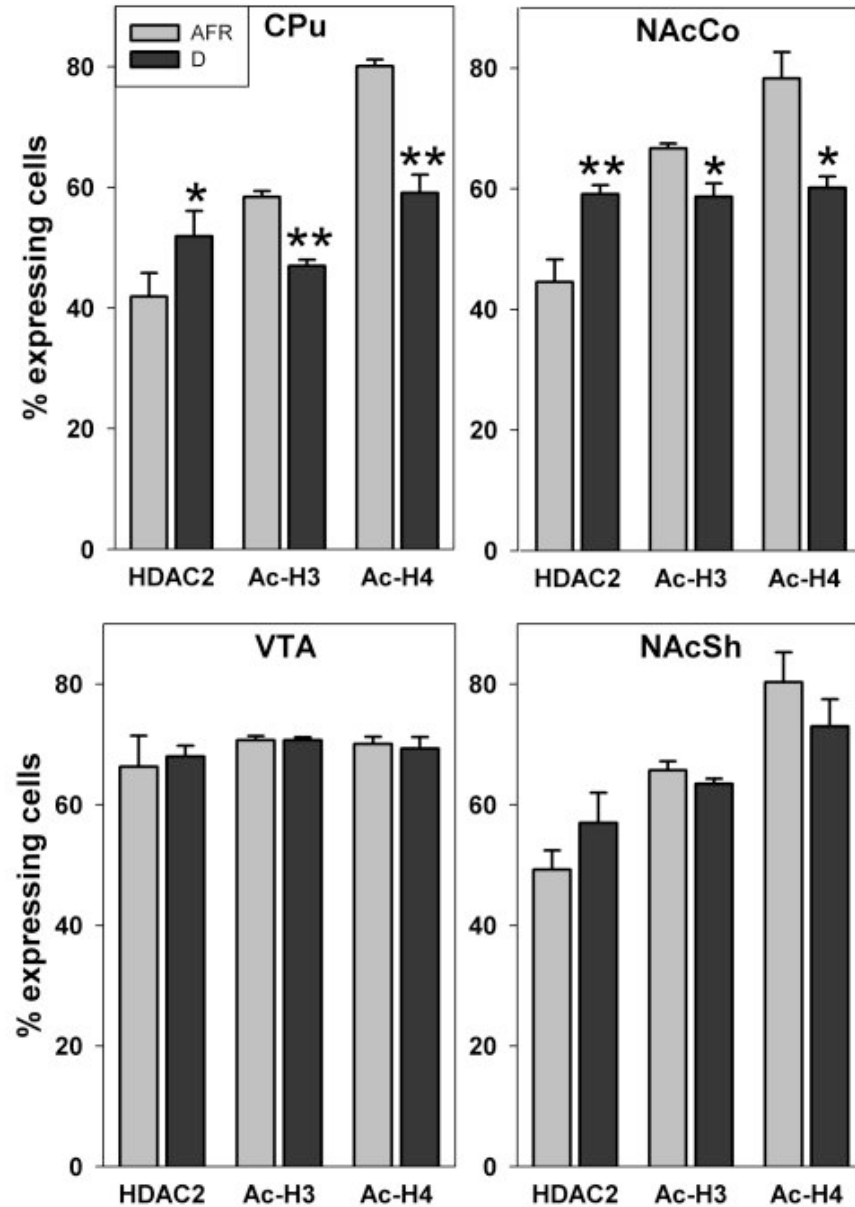


ND = AFR: control, D: deprived rats

CPu: caudate putamen nucleus  
 NAcCo: nucleus accumbens core  
 VTA: ventral tegmental area  
 NAcSh: nucleus accumbens shell

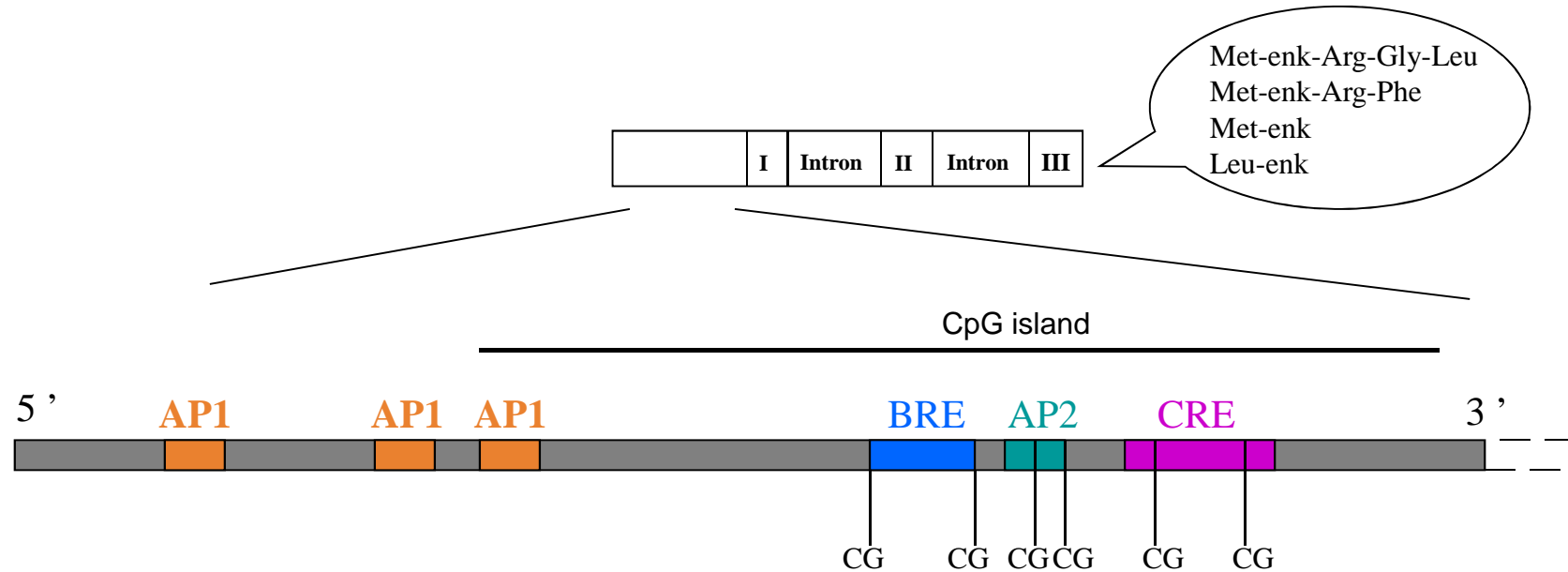
## Modèle de privation maternelle: HDAC2, Ac-H3, Ac-H4

■ AFR: control,  
■ D : deprived rats



Cpu: caudate putamen nucleus  
NAcCO: nucleus accumbens core  
VTA: ventral tegmental area  
NAcSh: nucleus accumbens shell

# Région promotrice du gène de la préproenképhaline

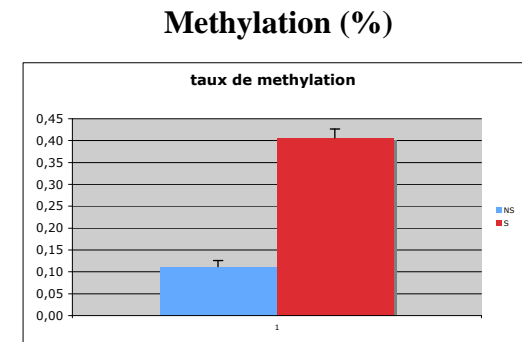
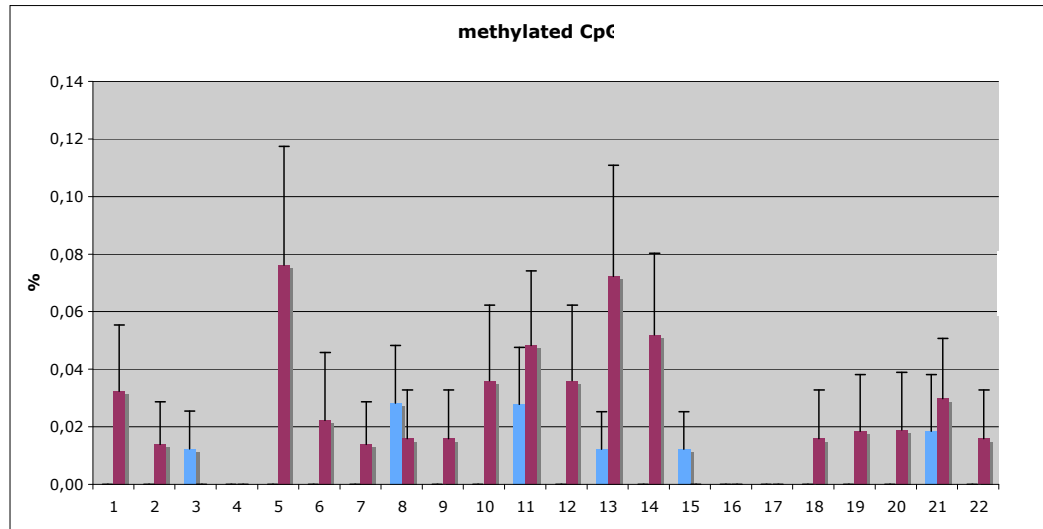


GATTGGTGGGGGAGCCTC<sup>1</sup>CGG<sup>2</sup>GCCCACT<sup>3</sup>GCACCC<sup>4</sup>GCCACCCT<sup>5</sup>CGGGGG 450  
<sup>6</sup>CCG<sup>7</sup>CGTGCTGTGGGA<sup>8</sup>CGTCCCCTCC<sup>9</sup>CGCCAGG<sup>10</sup>CGT<sup>11</sup>CGG<sup>12</sup>CGCGGGCTGGC<sup>14</sup> 500  
 GTAGGGCC<sup>15</sup>CGTCAGCTGCAG<sup>16</sup>CCGCTGG<sup>17</sup>CGATTGGGG<sup>18</sup>CGCGCG<sup>20</sup>CGCCT 550  
 CRE sp1 AP1/CRE  
<sup>22</sup>CCTTCGGTTTGGGGCTAATTATAAAGTGGCTGTGGCC.....

# Mapping of methylations on CpG island of PPE promoter

TTAGAGTTTTTAATTGATTGGTGGGGGAGTTTT**CGGC**GTTTATT**CGT**ATT**CGT**TATTTT**CGGGGGT****CGCGT**GTTGTGGGGAC**CGT**TTTTTTTT**CGTTA**

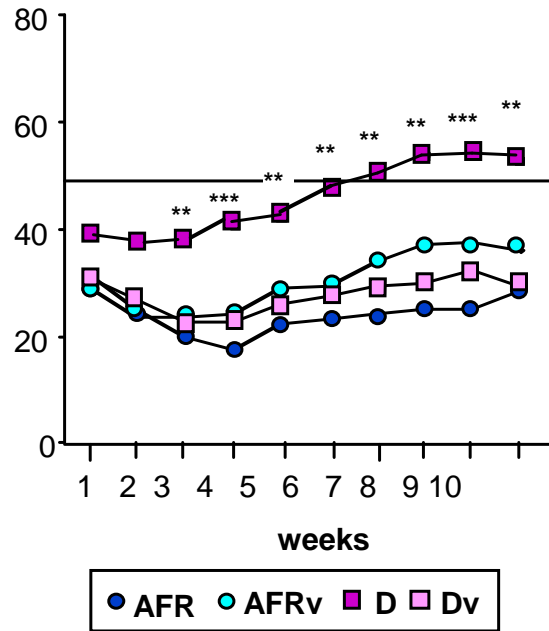
**GGCGT****CGGC****CGCGGGT**TGG**CGT**AGGGTTT**CGT**TAGTTGTAGTT**CGT**TGG**CGATT**GGGG**CGCGCGCGT**TTTTTTTT**CGG**TTTGGGGTTAATTATAAAGTGGT



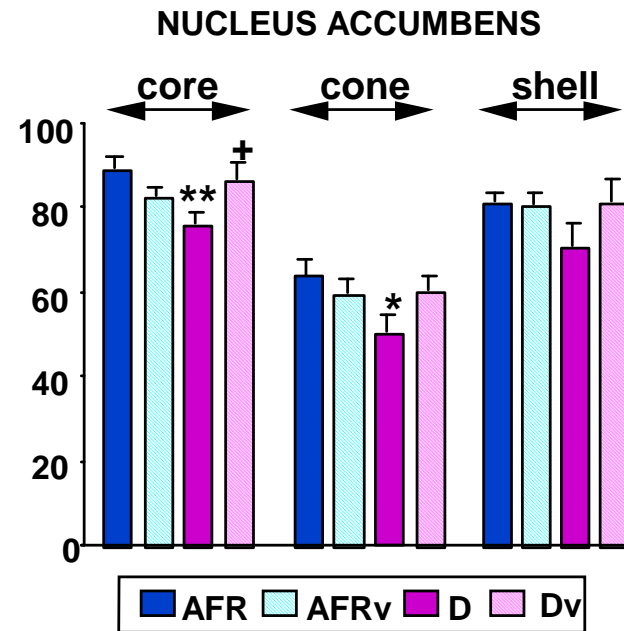
**ND = AFR: non deprived, D: deprived**

# How to cure it?

**ORAL MORPHINE  
SELF-ADMINISTRATION**

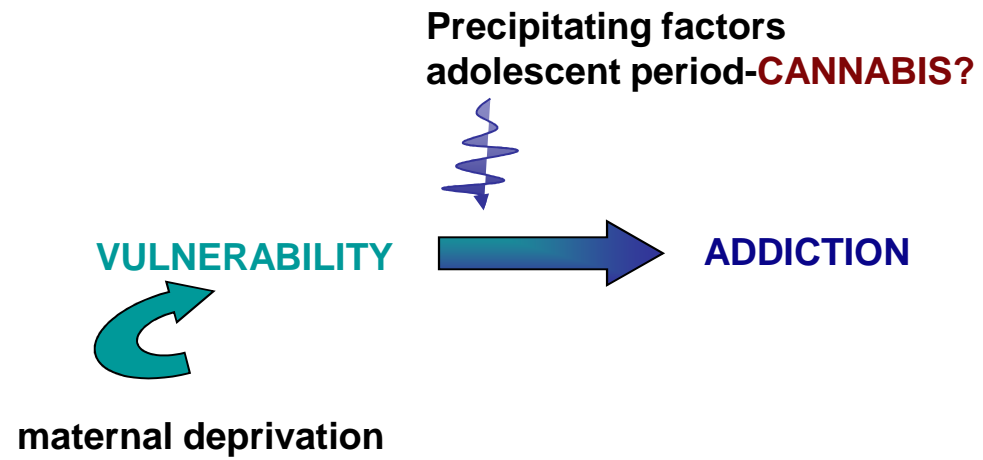


**Preproenkephalin mRNA**



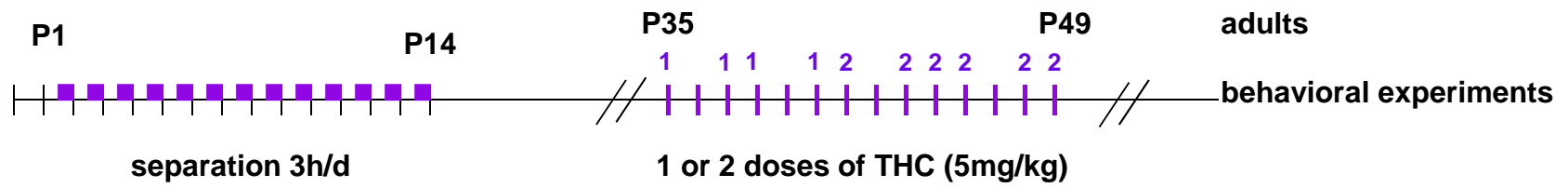
**Histone deacetylase inhibitor, sodium valproate  
chronic treatment (175 mg/kg i.p.)**

AFR= control, D: deprived rats, V: valproate

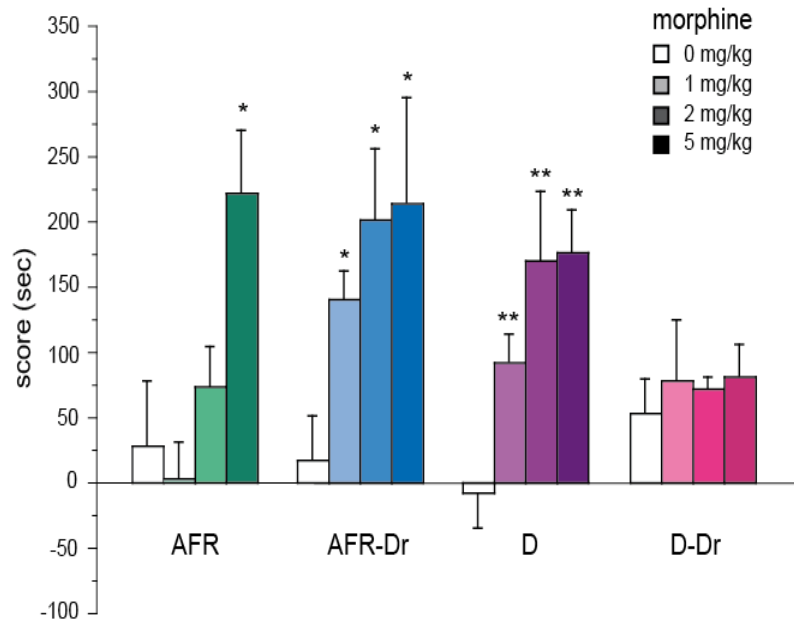




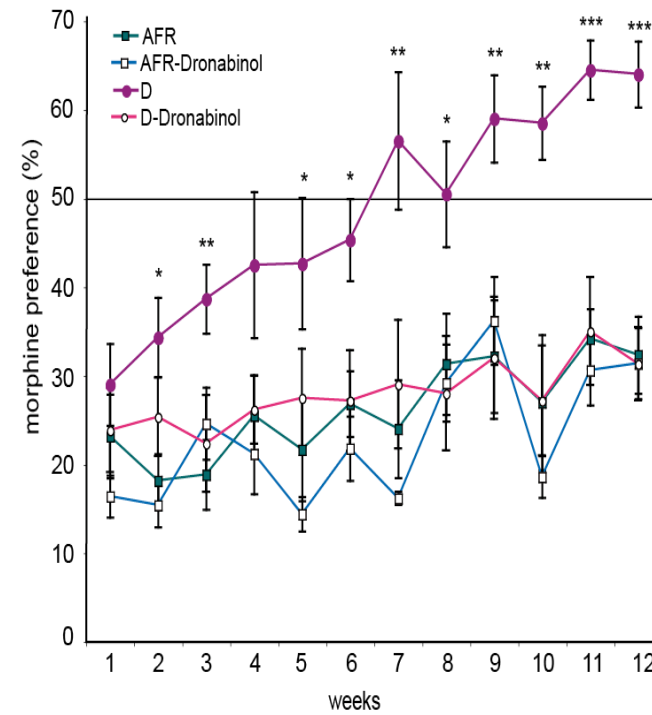
## Chronic THC exposure during adolescence



## MORPHINE PLACE PREFERENCE TEST

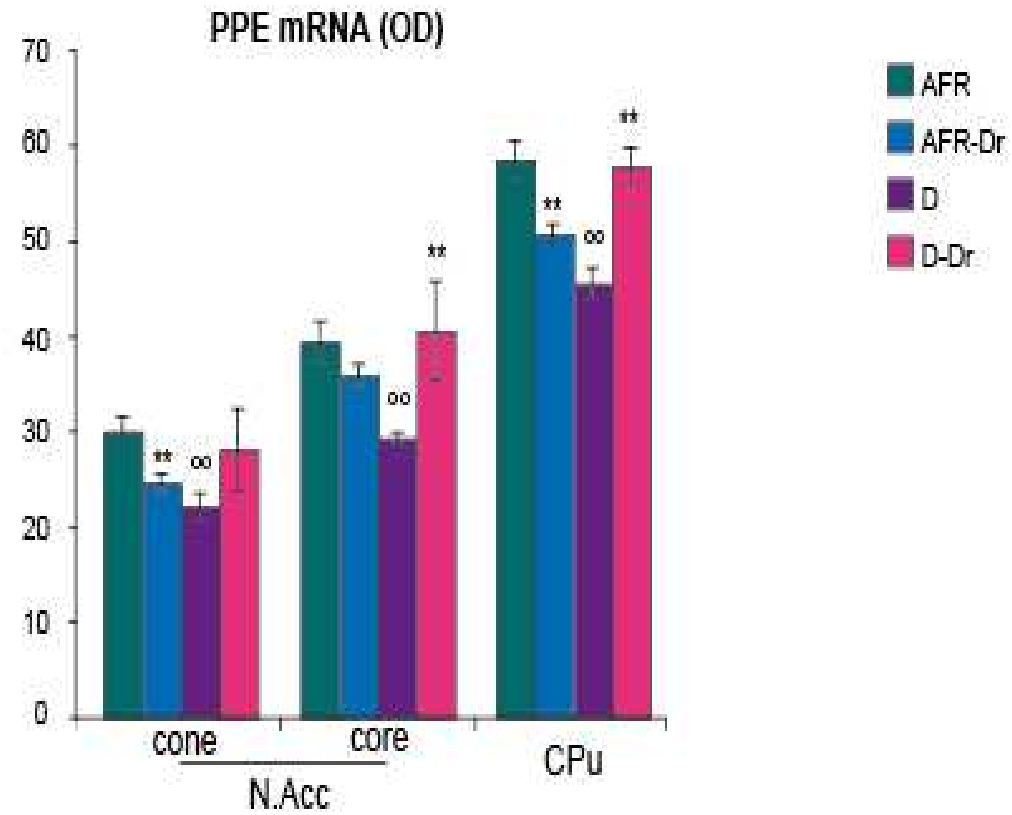


## ORAL AUTO-ADMINISTRATION morphine 25 mg/l



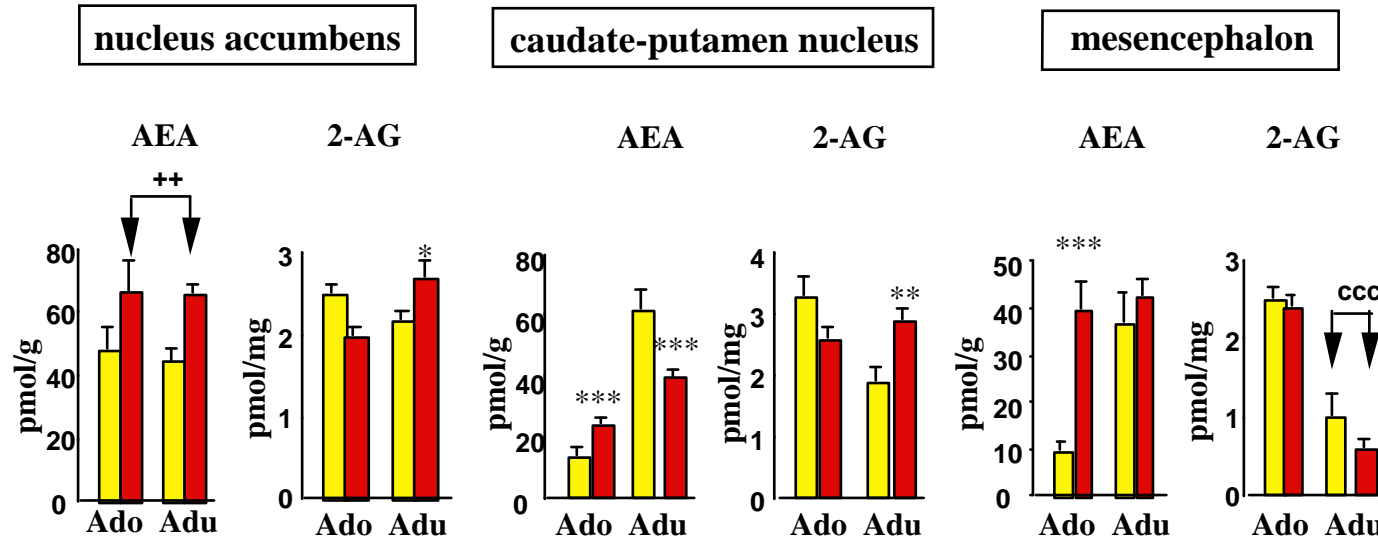
**Dr = dronabinol = THC, AFR = non deprived, D = deprived**

## PREPROENKEPHALIN mRNA LEVELS IN THE STRIATUM



Dr=dronabinol=THC agoniste partiel

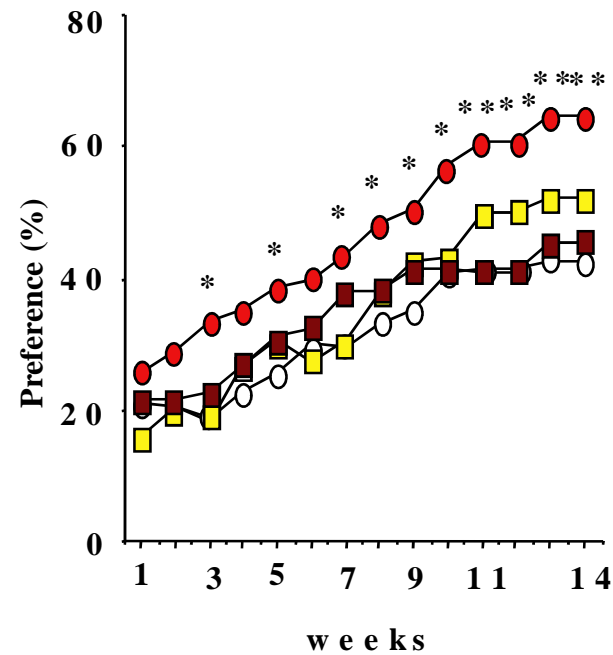
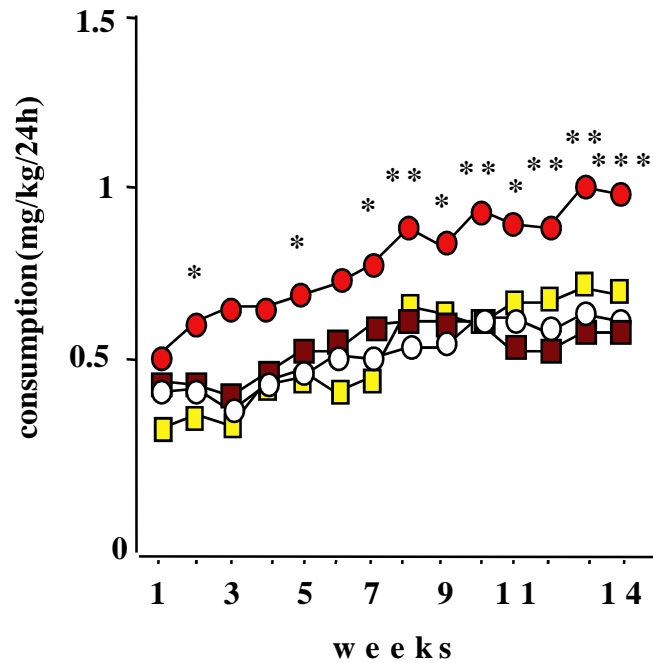
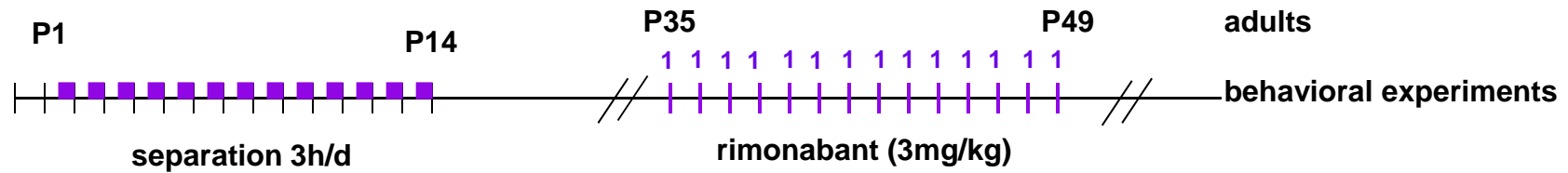
**Endocannabinoid levels in the striatum and the mesencephalon  
of non deprived ■ and deprived rats ■**



AEA = anandamide, 2-AG = 2-diacylglycerol  
Ado = adolescent, Adu = adult

*Collaboration V. DiMarzo*

# Effect of adolescent chronic treatment with CB1 antagonist rimonabant on morphine escalation behavior in maternally deprived rats.



○ AFR ● D ■ AFR-R ■ D-R

# MATERNAL DEPRIVATION

post-natal D1-D14



↗ MeCP2-HDAC preproenkephalin

Potential treatment

← HDACi



↘ striatal basal endogenous enkephalins

← THC-CB1 antagoniste



↗ anxiety ↗ stress reactivity }  
(cholecystokinin)



opiate dependence

← THC-CB1 antagoniste

**Intérêt du THC et antagonistes des récepteurs CB1**

**des inhibiteurs d'histone déacétylase**

**dans la dépendance aux opiacés**