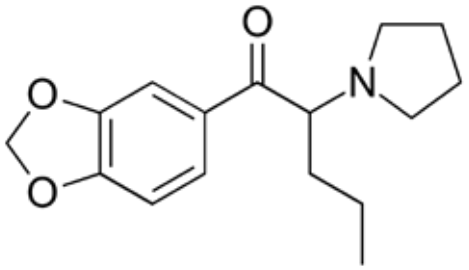
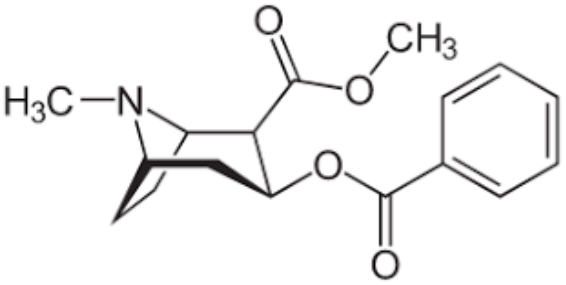




MDPV and Cocaine

„Fraternal but not identical twin sisters“

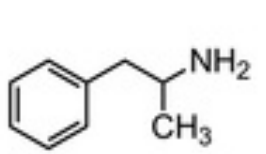
Brigitte Puster
Neuropsicofarmacologia dels derivats amfetamínics
Dra E. Escubedo, Dr D. Pubill

UNIVERSITAT DE BARCELONA

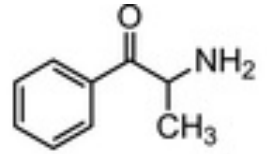
FACULTAT DE FARMÀCIA

Developement of the drug market

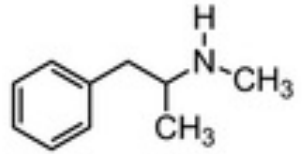
drug market



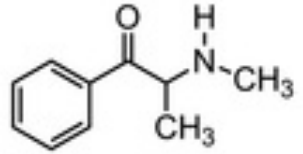
Amphetamine



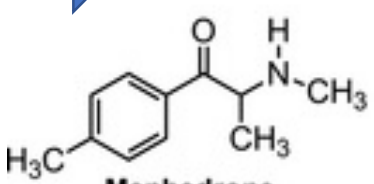
Cathinone



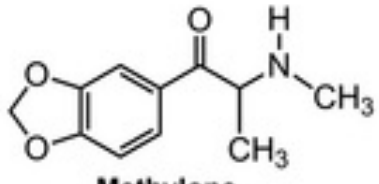
Methamphetamine



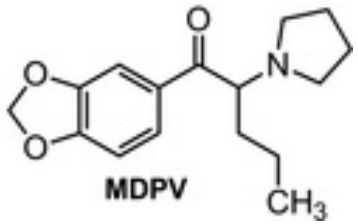
Methcathinone



Mephedrone

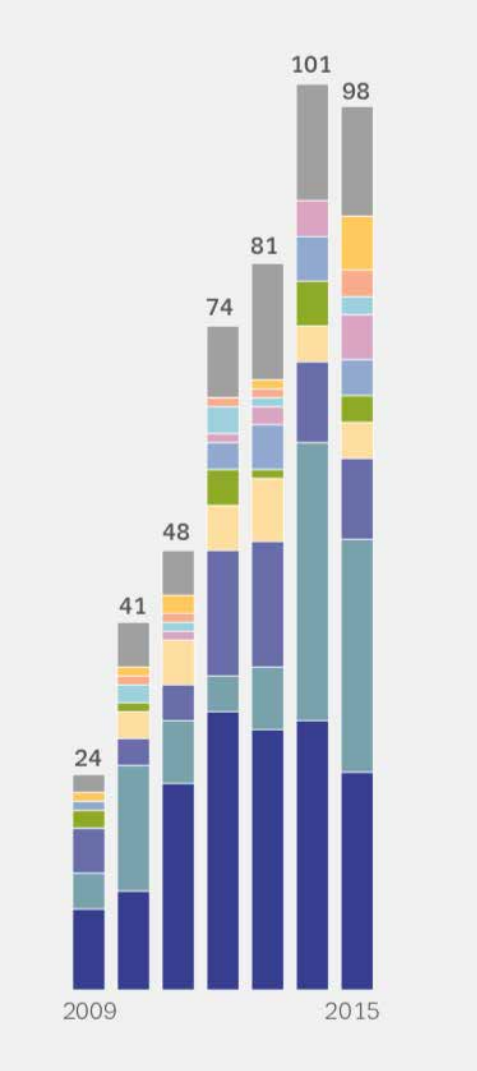


Methylone



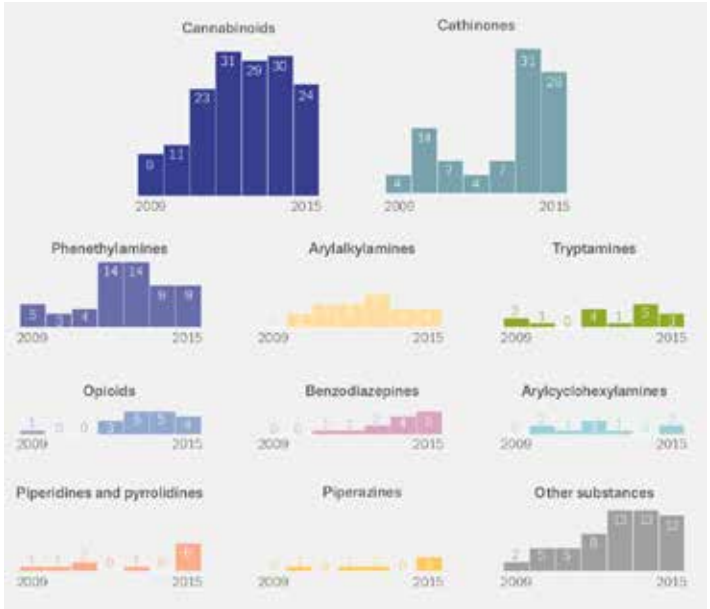
MDPV

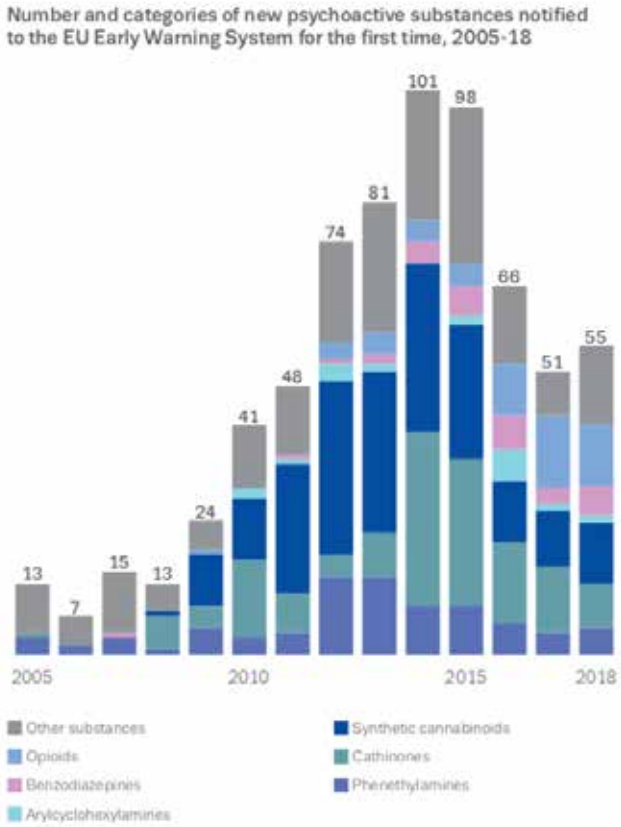
Development of the drug market



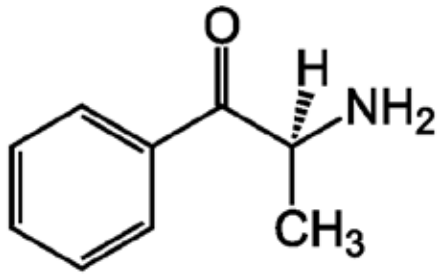
What are the main problems?

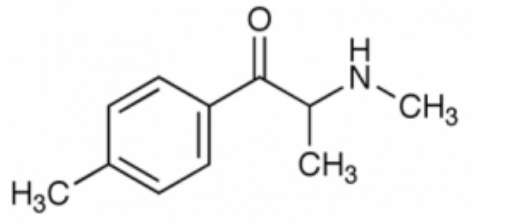
- Long time legal available
- Appearence of over 560 new substances of which 380 were discovered in only 5 years
- Cheaper
- Quality control/ dose
- Orderable over the internet
- Synthetically producible
- Purity





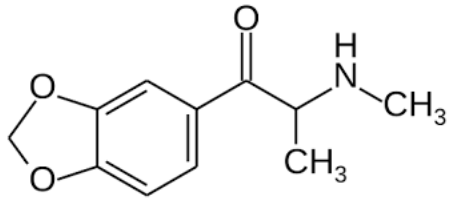
Synthetic cathinones





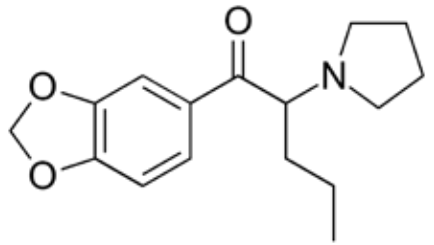
Mephedrone

„Meow-meow“



Methylone

„explosion“



MDPV

„Cannibal drug“

British Journal of Pharmacology

British Journal of Pharmacology (2017) **174** 1161–1173 1161

RESEARCH PAPER

Exposure of adolescent mice to 3,4-methylenedioxypyrovalerone increases the psychostimulant, rewarding and reinforcing effects of cocaine in adulthood

Correspondence Dr Olga Valverde, Neurobiology of Behaviour Research Group (GReNeC), Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Dr Aiguader 88, Barcelona 08003, Spain. E-mail: olga.valverde@upf.edu

Received 18 December 2016; **Revised** 21 February 2017; **Accepted** 24 February 2017

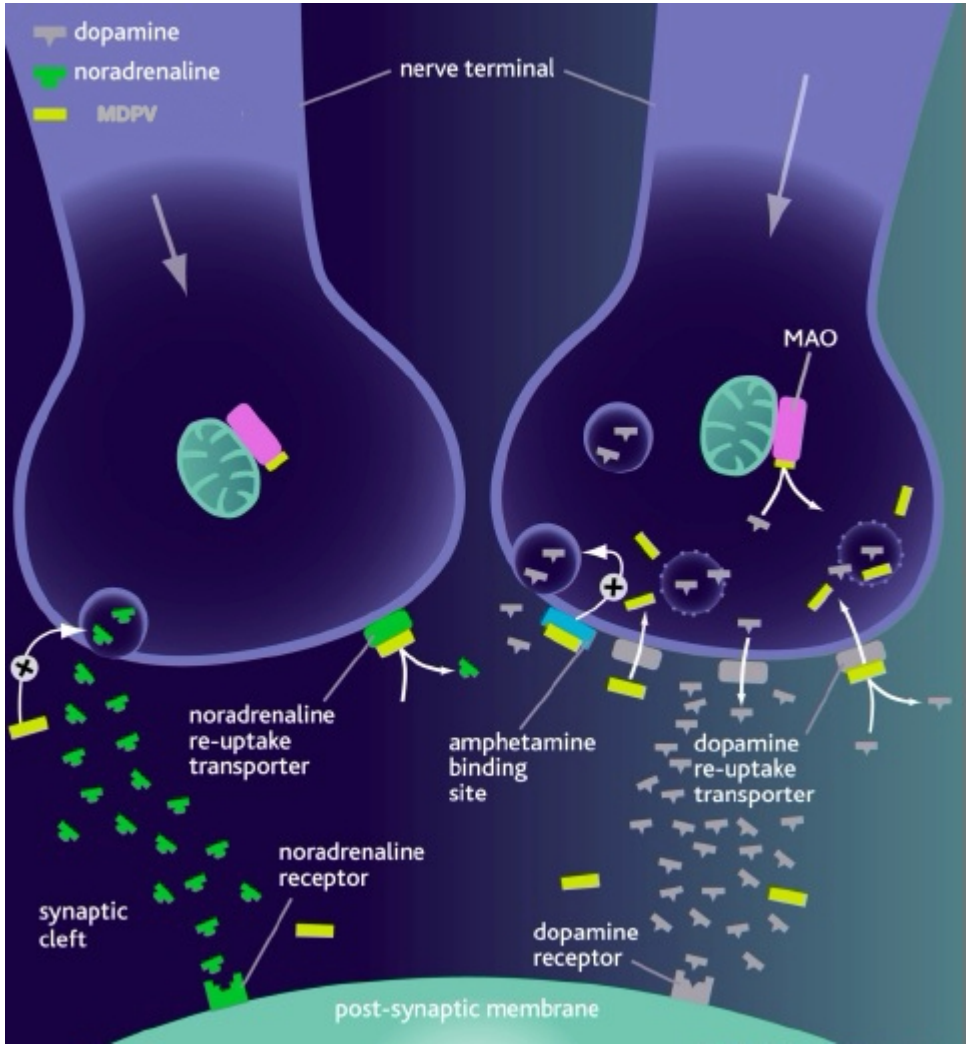
R López-Arnau[1,*], M A Luján[2,*], L Duart-Castells[1], D Pubill[1], J Camarasa[1], O Valverde[2,3] and E Escubedo[1]

[1]*Department of Pharmacology and Therapeutic Chemistry, Pharmacology Section and Institute of Biomedicine (IBUB), Faculty of Pharmacy, University of Barcelona, Barcelona, Spain,* [2]*Neurobiology of Behaviour Research Group (GReNeC-NeuroBio), Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain, and* [3]*Neuroscience Research Programme, IMIM-Hospital del Mar Research Institute, Barcelona, Spain*

*Equally contributed.

It seems like these two drugs behave as fraternal, but not as identical twin sisters

Methylendioxypyrovalerone (MDPV)



- Selective Catecholamine transporter blocker
- MDPV is more selective for DA system:
  - 50-fold more potent at DAT
  - 10- fold more potent at NET
  - 10-fold less potent at SERT
- More potent in inducing locomotor activation

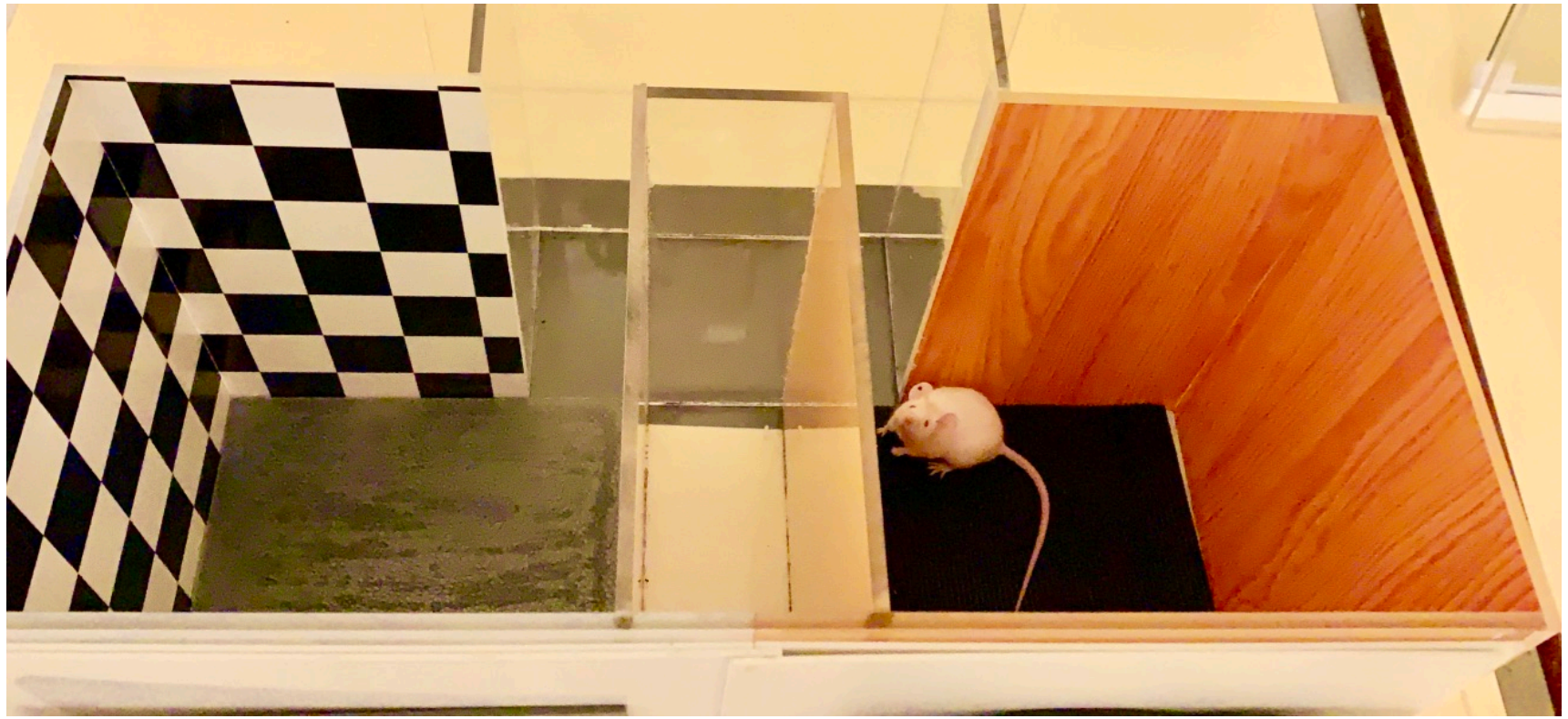
The aim is to determine the cross reactivity in the rewarding test of Conditioned place preference

Conditioned place preference

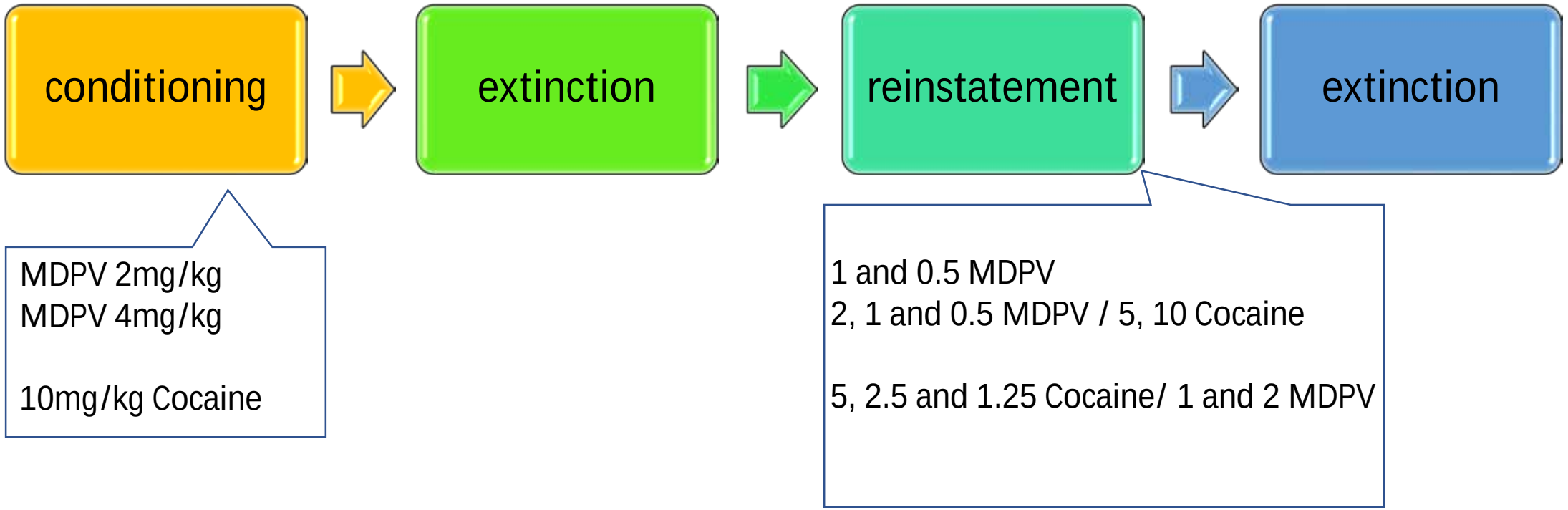
Day 1 pretest

Day 2-5 conditioning phase

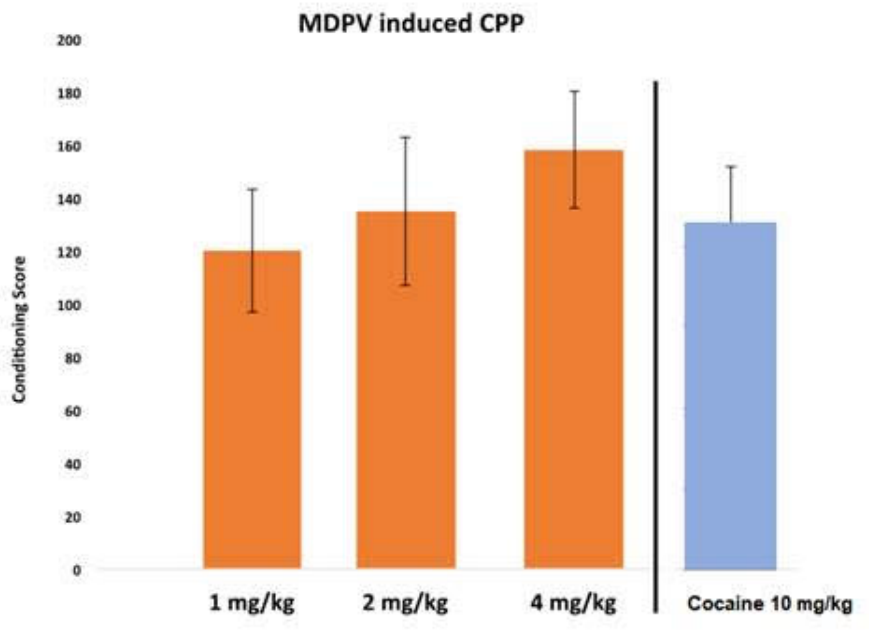
Day 6 test -> preference score

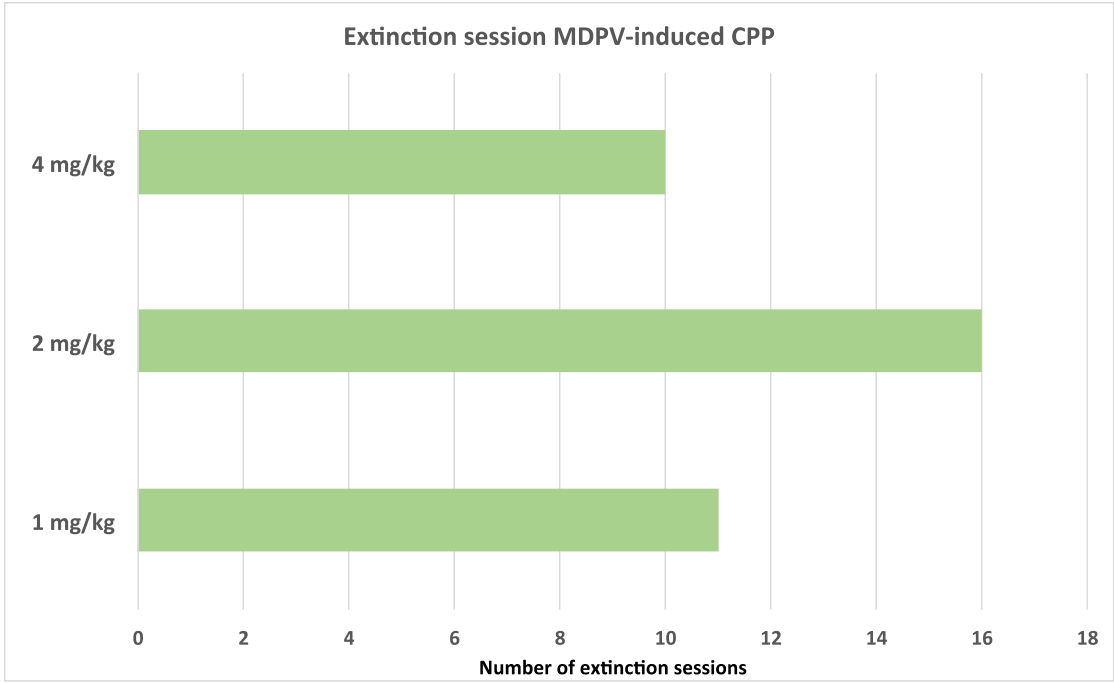


Experimental design

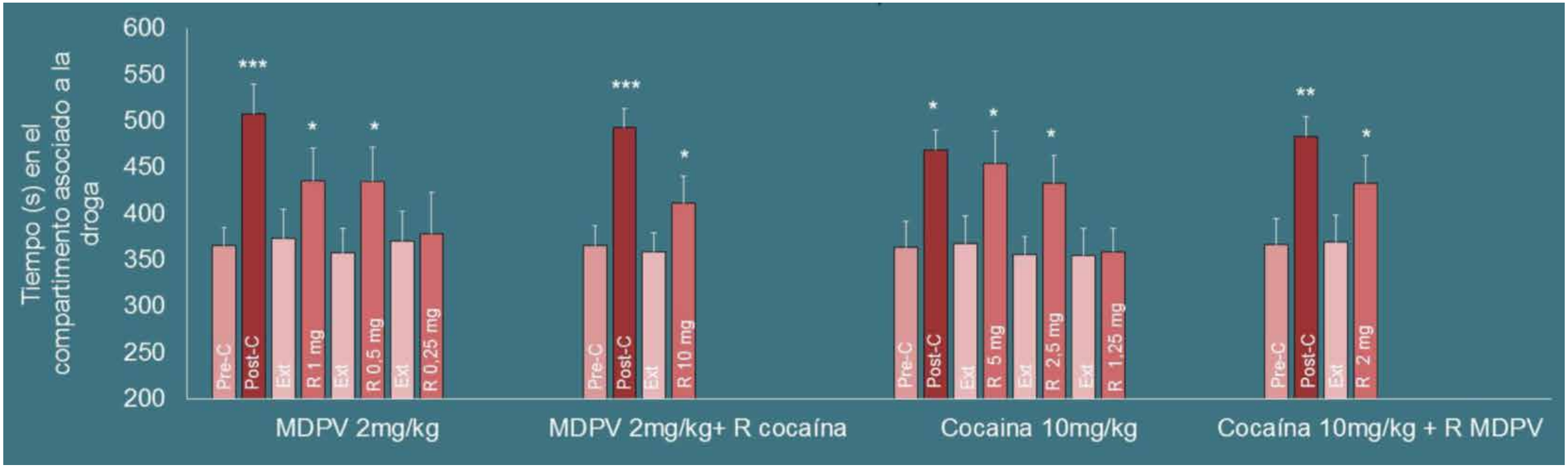


Extinction sessions with MDPV



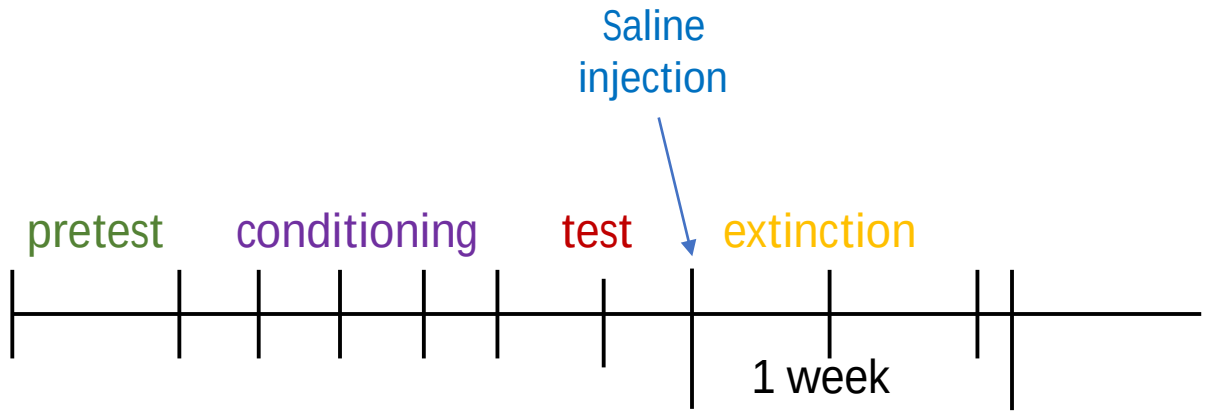


CPP results of Cross CPP



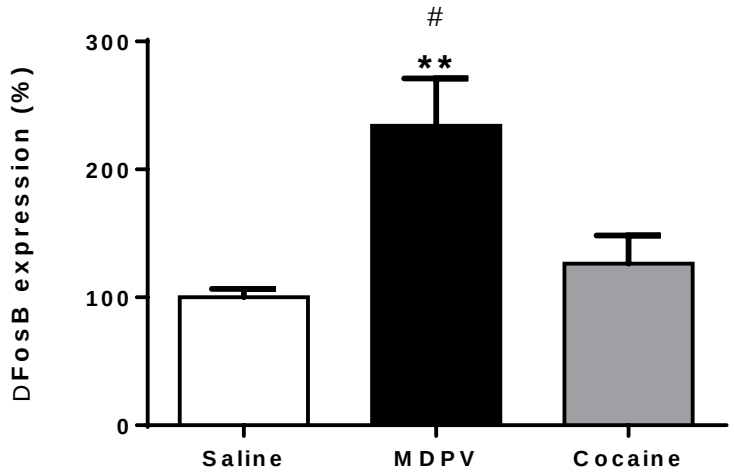
Positive response to the other drug

Analysis of the parameters



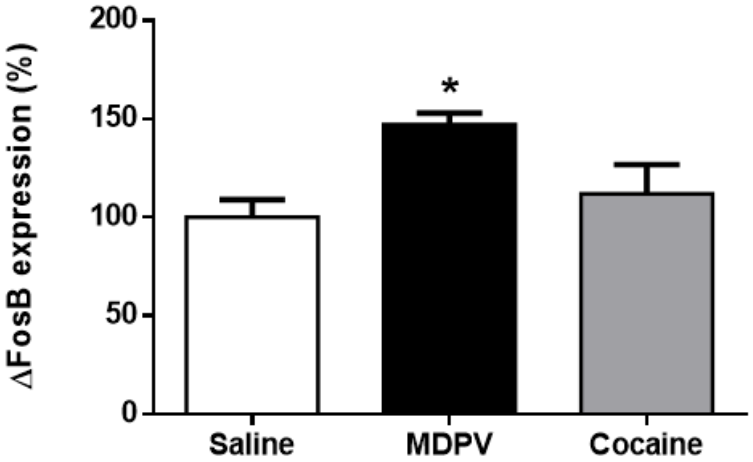
24h after CPP sacrif
Delta FosB,
CB1,
Arc,
G9a

Expression of delta Fos B



24 hours after CPP

** p < 0.05 vs Saline
# p < 0.01 vs Cocaine



1 week after CPP

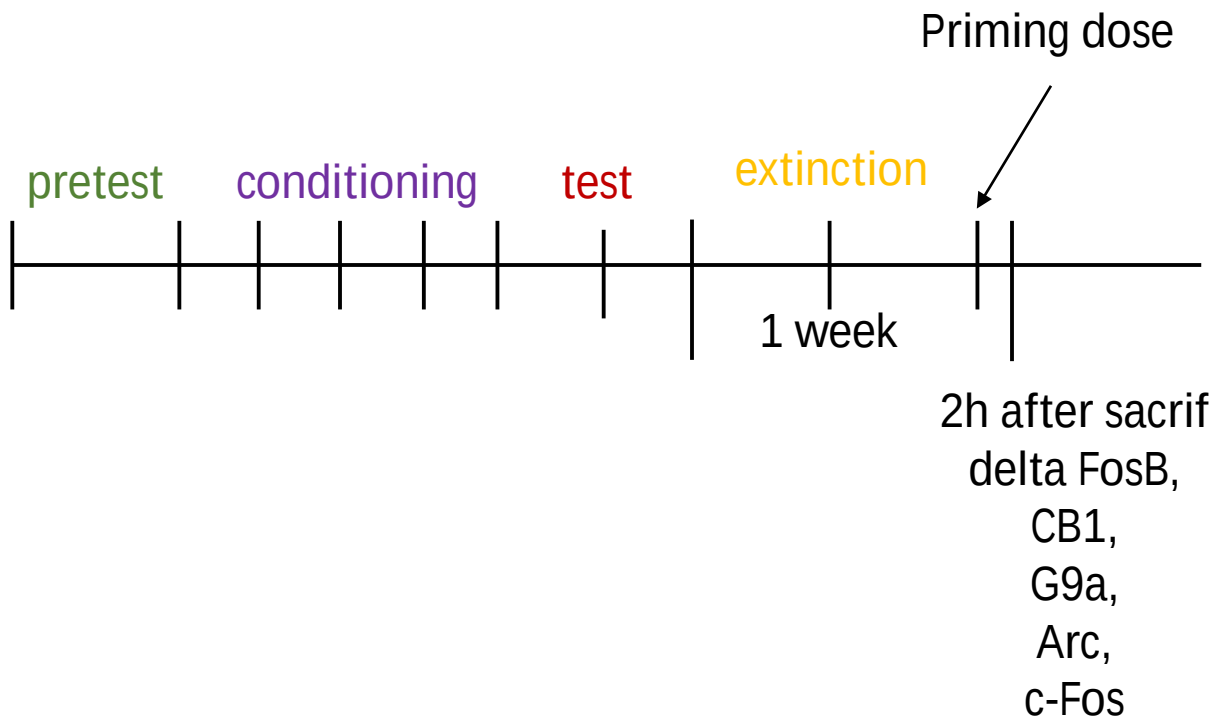
* p < 0.05 vs Saline

MDPV 2 mg/kg
16 sessions

>

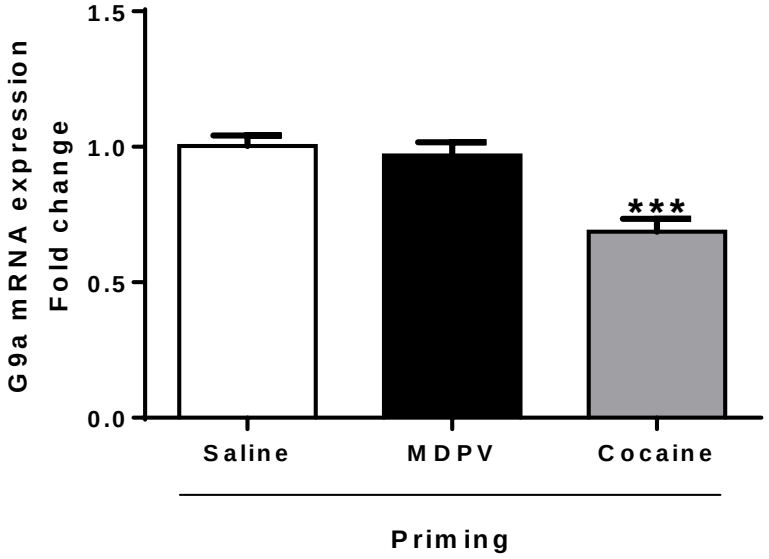
Cocaine 10 mg/kg
6 sessions

Analysis of the parameters



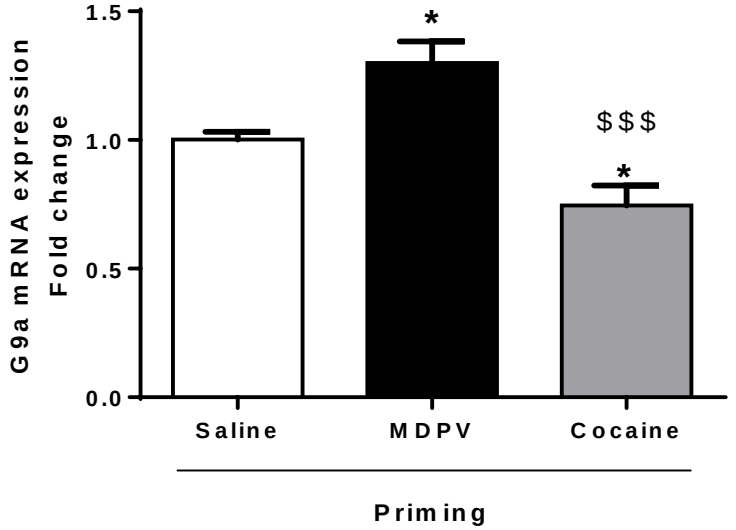
G9a expression after priming dose of MDPV, Cocaine and Saline

MDPV-conditioned (2mg/kg)



*** p < 0.001 vs Saline

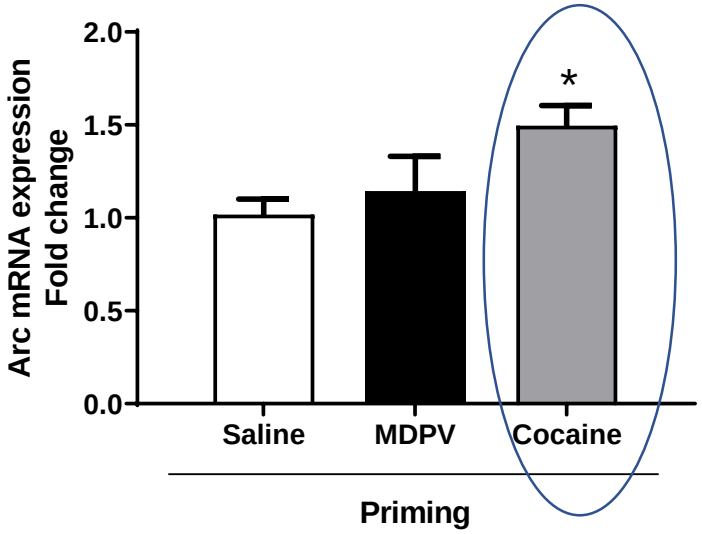
Cocaine-conditioned (10mg/kg)



* p < 0.05 vs Saline
$$$ p < 0.001 vs MDPV

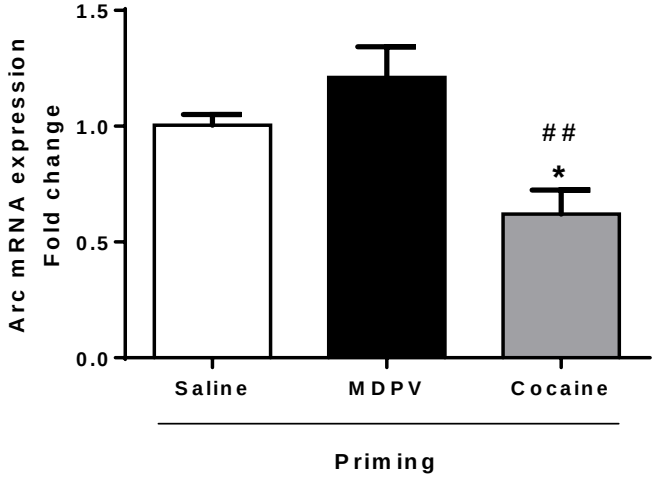
ARC expression after priming dose of MDPV, Cocaine and Saline

MDPV-conditioned (2mg/kg)



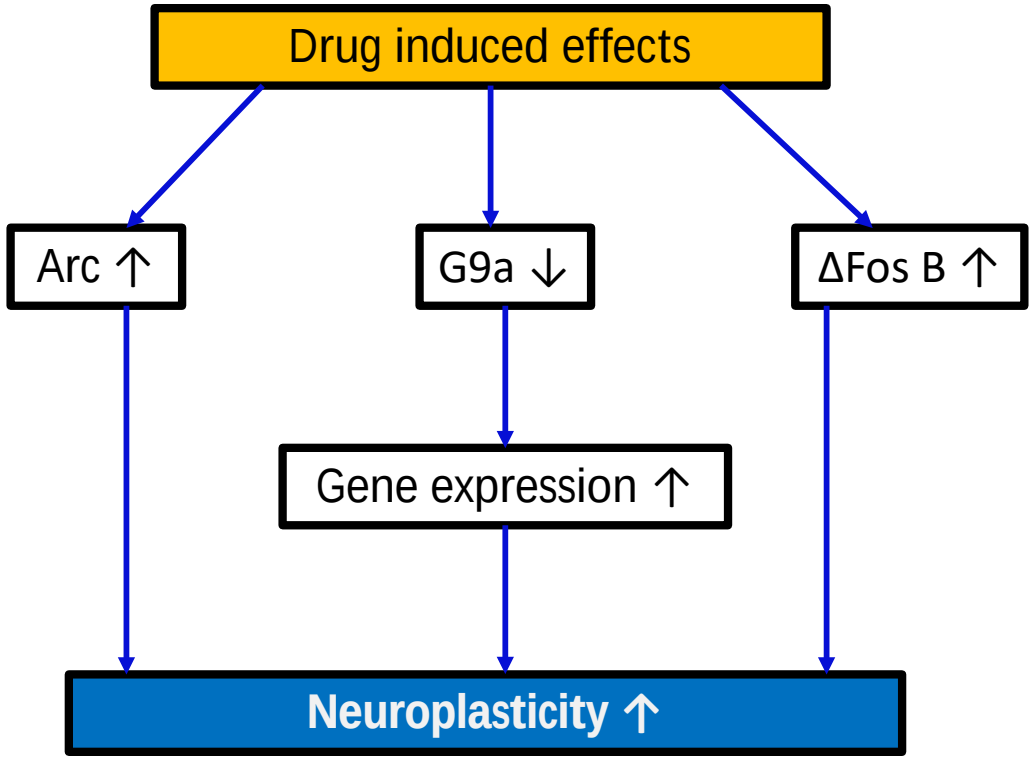
- ΔFosB
- G9a

Cocaine-conditioned (10mg/kg)

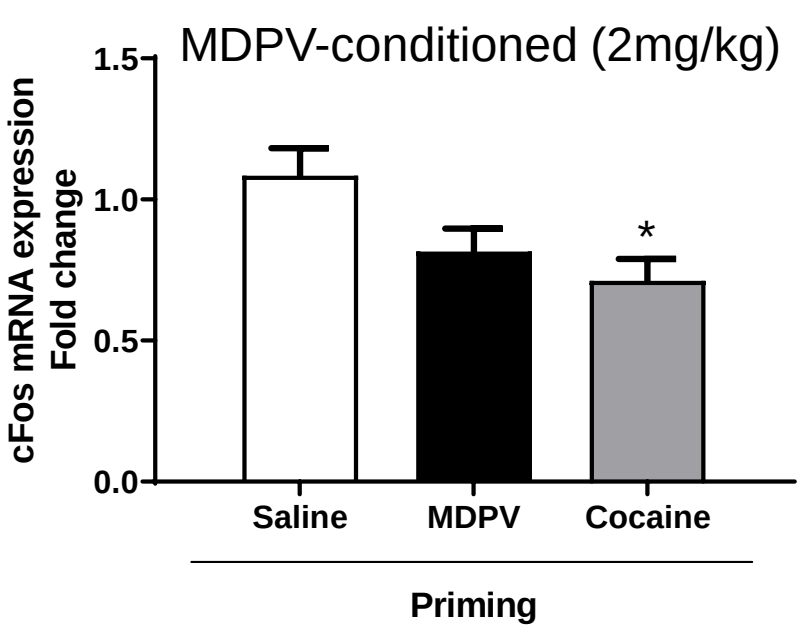


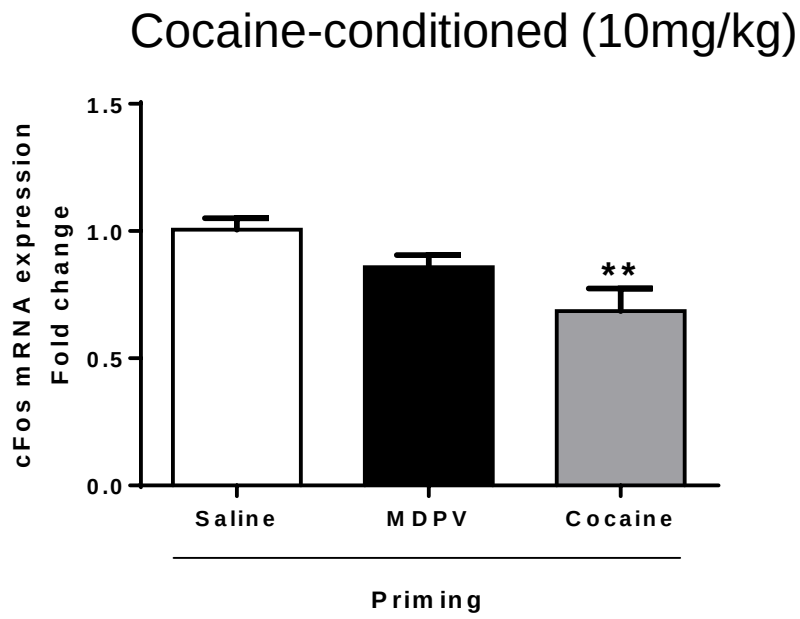
*p<0.05 vs saline priming
##p<0.01 vs MDPV priming

Neuroplasticity



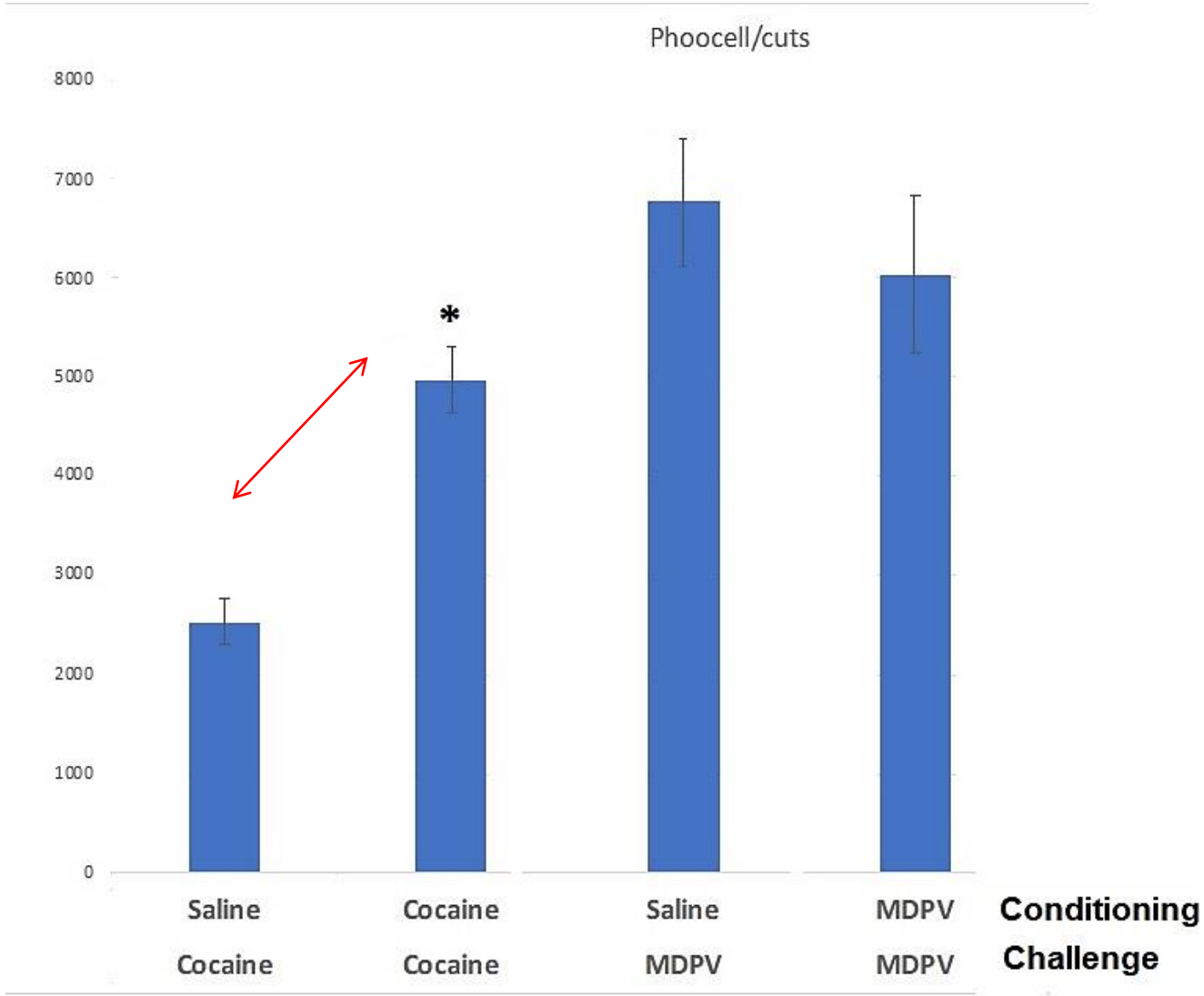
cFos expression after priming dose of MDPV, Cocaine and Saline





Todtenkopf et al 2009:
↓ cFos ⇔ locomotor sensitization

↓ cFos ⇔ locomotor sensitization



10 mg/kg 2 mg/kg

Conclusion

- MDPV is a more potent psychostimulant than Cocaine. The equieffective doses in locomotor activity are 1mg/kg of MDPV and 10 mg/kg of Cocaine
- MDPV has a rewarding effect at 1, 2, 4 mg/kg evidenced in CPP
- The equieffective doses in a CPP are 2mg/kg of MDPV and 10mg/kg of Cocaine
- The extinction time is longer for MDPV than Cocaine. This correlates with a significant expression of deltaFosB in MDPV group that lasts for a week.
- Both drugs reinstated the rewarding effect after a dose of the same or the other drug

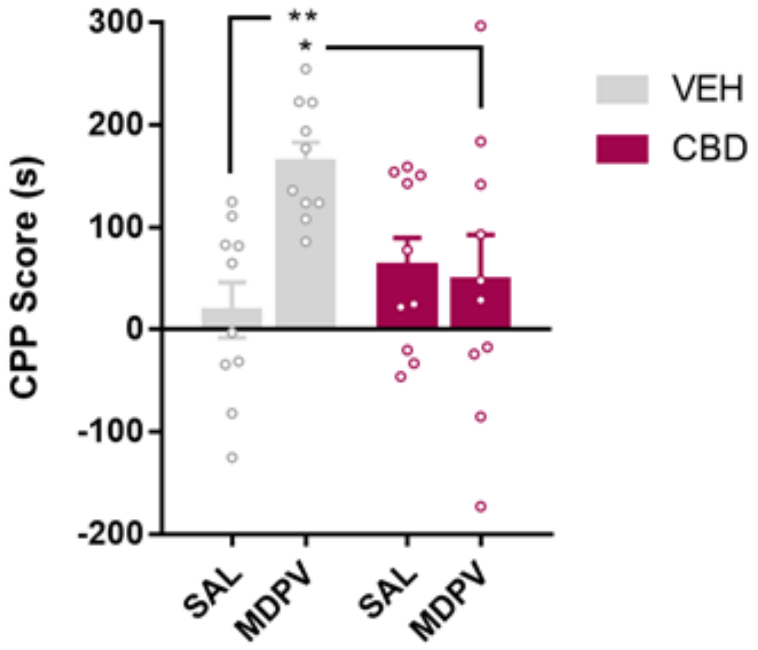
Conclusion

- Cocaine, but not MDPV, decreases the early expression of G9a, regardless of how the animals have been conditioned.
- Animals conditioned with MDPV:
  - When challenged with the same drug showed no effects indicative of plasticity.
  - However, when challenged with cocaine, the changes in the factors related with neuroplasticity point to an activation of this neuronal process
- Cocaine priming dose always decreased c- Fos and evidenced a sensitization effect, independently of the conditioning drug. Priming with MDPV did not produce enough decrease in cFos to induce sensitization.

Final Conclusion

- Independently of the potency of the reinforcing effects of both substances, both are able to sensitize the reinforcement system to the point of reinstating the preference with a substance different from that with which it is preferred.
- Our results indicate that after a chronic abuse of MDPV, reinstatement with cocaine would trigger an important neuroplasticity, implying a stronger vulnerability to cocaine dependence

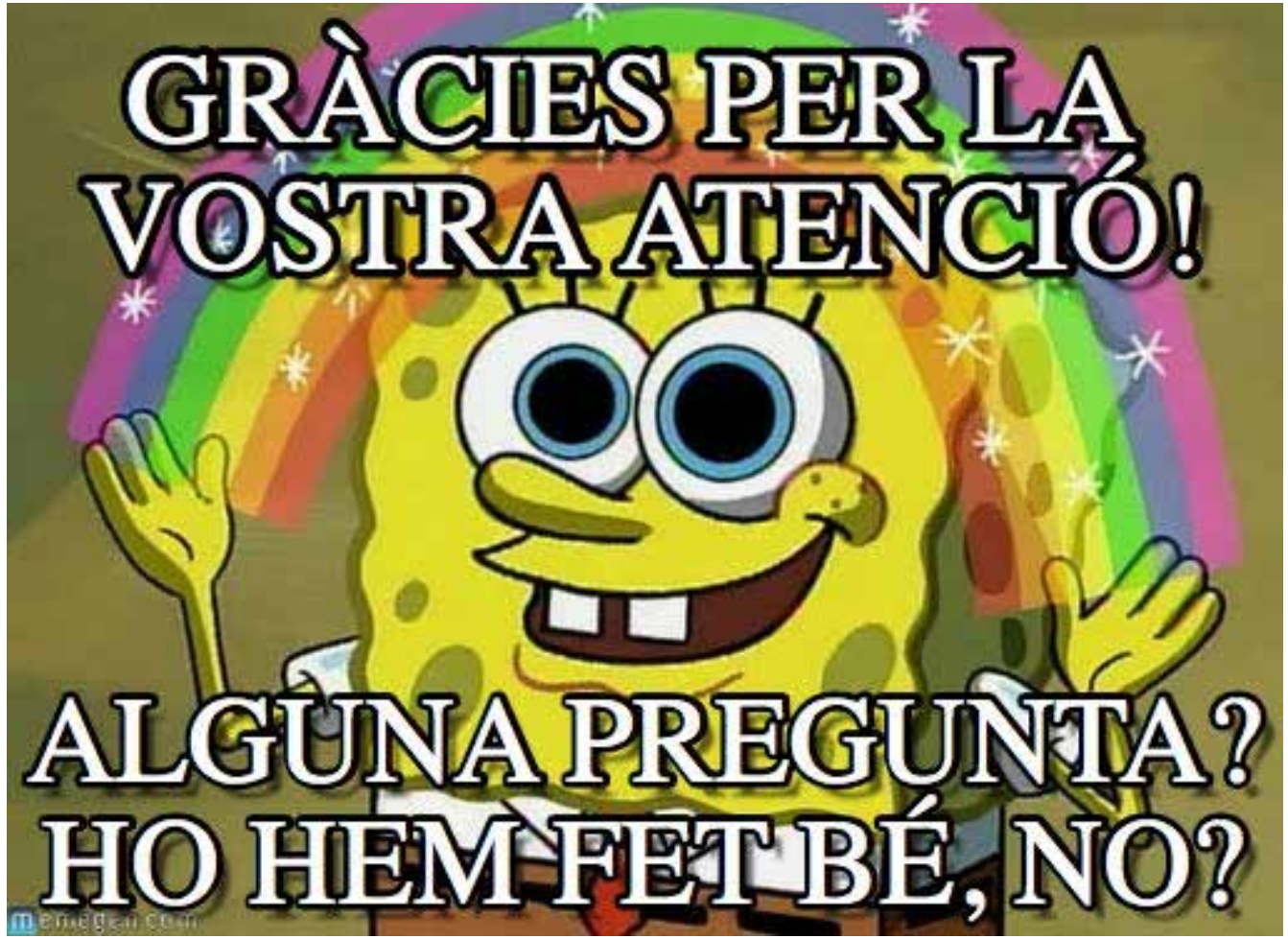
CPP with MDPV and CBD



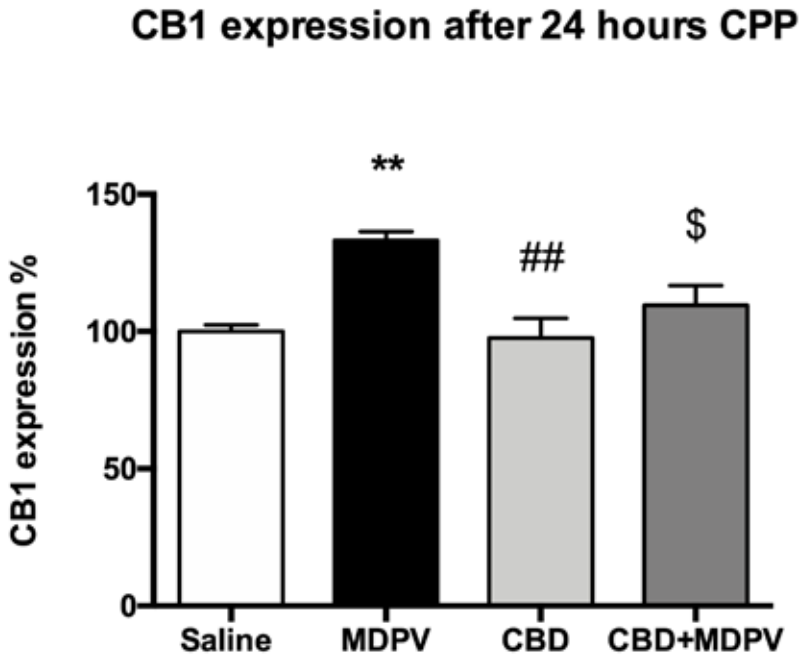
Cannabidiol 20mg/kg i.p
MDPV 2mg/kg i.p.

30 min before CPP
directly before

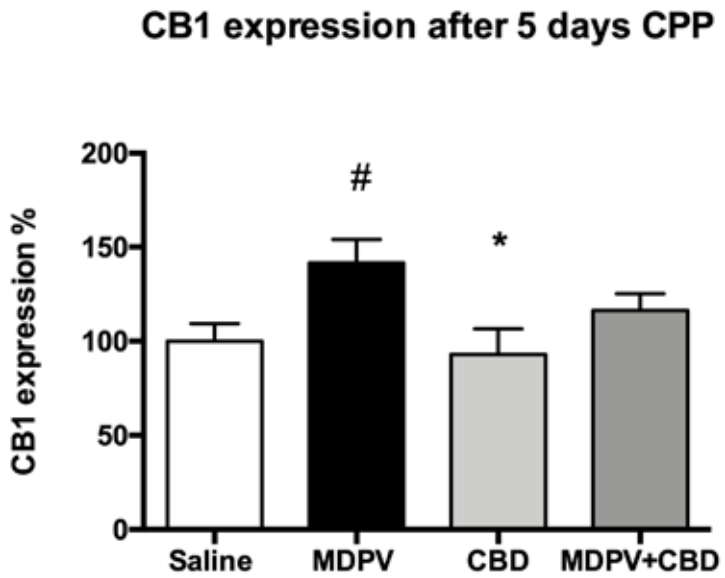
- Saline: • Saline
- Saline: • MDPV
- CBD: • Saline
- CBD: • MDPV


GRÀCIES PER LA VOSTRA ATENCIÓ!
ALGUNA PREGUNTA?
HO HEM FET BÉ, NO?

CB 1 expression induced by CBD/MDPV



** p < 0.01 vs Saline
p < 0.01 vs MDPV
$ p < 0.05 vs MDPV



* p < 0.05 MDPV vs CBD

# p < 0.05 MDPV vs Saline