THE ROLE OF α7 NICOTINC RECEPTORS IN REINSTATEMENT OF DRUG INDUCED CONDITIONED PLACE PREFERENCE

M.Giulia COCCIA [1], Sue WONNACOTT[2], David HEAL[3], Christopher P. BAILEY[1]

1: Pharmacy and Pharmacology, University of Bath; 2: Biology & Biochemistry, University of Bath; 3: RenaSci LTD, Nottingham

INTRODUCTION

Chronic exposure to drugs of abuse induces the formation and maintenance of maladaptive drug cue–context associations that can induce relapse. The ventral hippocampus (vHip) is involved in associative memory and drug-related emotional behaviours, and has been implicated in drug- and cue-induced relapse. The cholinergic system plays a key role in neuronal activity and synaptic plasticity in the vHip [1]. Inhibiting α7 nicotinic acetylcholine receptors (α7 nAChRs) in vHip with the antagonist methyllycaconitine (MLA) selectively attenuated priming-induced reinstatement in morphine conditioned place preference (CPP) [2].

AIMS

- To investigate if α7 nAChRs contribute to heroin- and cocaine-CPP in mice.
- To examine c-Fos expression in vHip after drug priming-induced reinstatement.
- To determine if MLA administered before heroin, cocaine or saline affects c-Fos expression in the absence of drug-conditioning.

RESULTS: HEROIN-INDUCED CPP REINSTATEMENT AND C-FOS EXPRESSION IN VHIP IN MLA-TREATED MICE AND SALINE CONTROLS

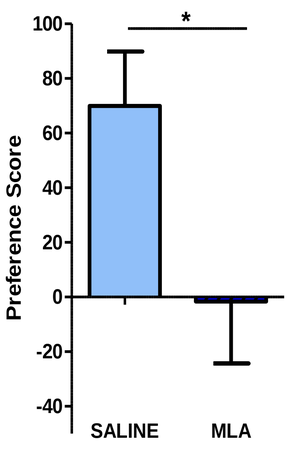


Fig. 1 – MLA abolished reinstatement of heroin-induced CPP – All mice acquired preference for the heroin-paired chamber and CPP was then extinguished. No significance differences were observed in Preference or Extinction scores between saline and MLA groups (not shown).
- MLA administered prior to heroin-priming abolished heroin-induced reinstatement of CPP (SALINE: N=8; MLA: N=8; *=p<0.05 Student's t-test).

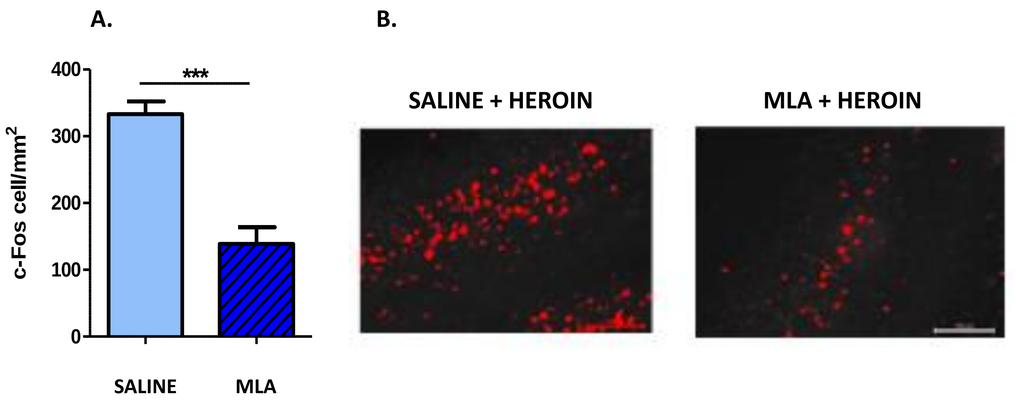


Figure 2 – MLA decreased c-Fos expression after heroin-primed CPP reinstatement in the vHip
A. Administration of MLA prior to heroin-primed reinstatement significantly reduced c-Fos expression in vHip compared to animals administered saline prior to heroin-primed reinstatement (SALINE: n=4; MLA: n=4; ***=p<0.001 Student's t-test).
B. Representative coronal sections of mouse brain, at the level of the vHip, stained for c-Fos.

RESULTS: COCAINE-INDUCED CPP REINSTATEMENT AND C-FOS EXPRESSION IN VHIP IN MLA-TREATED MICE AND SALINE CONTROLS

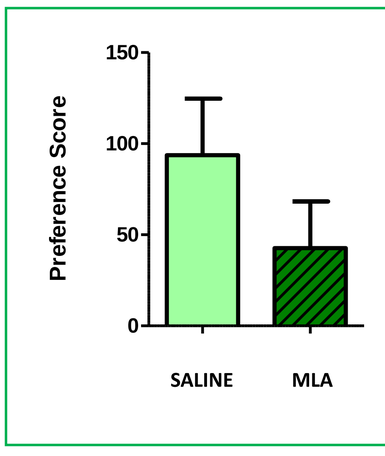


Figure 3 – The effect of MLA on reinstatement of cocaine induced-CPP – All mice acquired preference for the drug-paired chamber and then extinction. MLA administered prior to cocaine-priming had no significant effect on reinstatement of CPP (SALINE: n=8; MLA: n=7; p>0.05 Student's t-test).

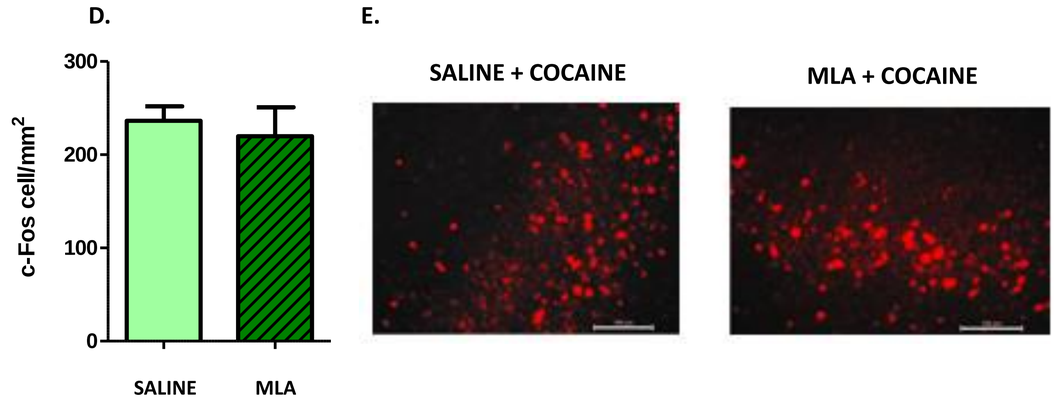


Figure 4 – MLA did not reduce c-Fos expression after cocaine-primed CPP reinstatement
D. Cocaine-primed CPP reinstatement induced robust cFos expression in the vHip. There was no significant effect of MLA administered prior to cocaine-priming (SALINE: n=6; MLA: n=7; p>0.05 Student's t-test)
E. Representative images as above.

RESIULTS: C-FOS EXPRESSION IN VHIP IN NON-CONDITIONED MICE

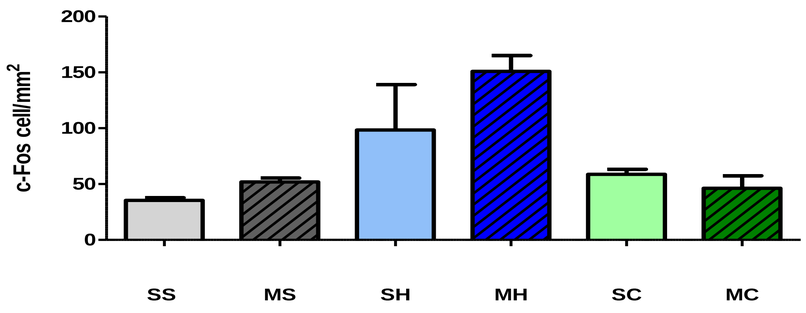


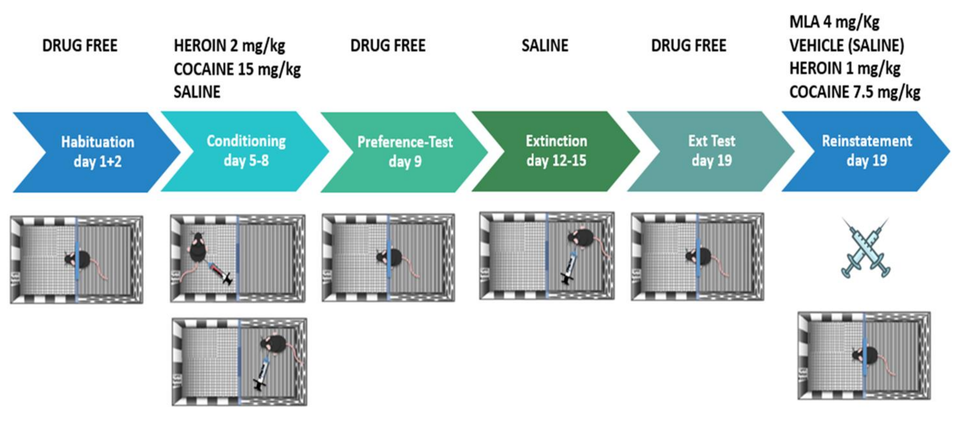
Figure 5 – MLA did not affect c-Fos expression in naive mice given a single injection of drug or saline
– Heroin, but not cocaine, increased cFos expression in the vHip .
- There was no significant difference in c-Fos expression in mice pre-treated with MLA or SALINE 20 min before receiving SALINE, HEROIN OR COCAINE (SALINE-SALINE, SS: n=2; MLA-SALINE, MS: n=3; SALINE-HEROIN, SH: n=5; MLA-HEROIN, MH: n=2; SALINE-COCAINE, SC: n=5; MLA-COCAINE, MC; n=3; p>0.05 One-Way ANOVA, Bonferroni's Multiple Comparison Test).

CONCLUSIONS

- Reinstatement of heroin-CPP and c-Fos expression in the vHip in mice were inhibited by MLA. This suggests blockade of α7 nAChRs reduces reinstatement-induced neuronal activation in the vHip.
- In contrast, MLA did not significantly affect cocaine-primed CPP reinstatement or c-Fos expression. However, the experiment needs to be repeated with a larger sample and it is also possible that the cocaine dose used was too high. Further studies with different cocaine doses will be performed.
- MLA had no effect on c-Fos expression in vHip when given before heroin, cocaine or saline in naïve mice. Hence, MLA has no effect *per se* on c-Fos activity, or on any drug-induced changes. Its effect appears specific to reinstatement, highlighting the role of α7 nAChRs in recalling addiction-related memories.
- We speculate that α7 nAChRs may influence glutamate synapse plasticity in the vHip and electrophysiological experiments will be performed to study the modulation of synaptic plasticity induced by these receptors in the vHip.

MATERIALS AND METHODS

32 male C57BL/6J mice (16 per experiment) underwent heroin- or cocaine-induced CPP (heroin: 2 mg/kg, i.p; cocaine 15 mg/kg i.; saline 0.9%), followed by extinction training. Drug-primed reinstatement was induced by a single injection of heroin (heroin:1 mg/kg, i.p.; cocaine: 2 mg/kg i.p;) with prior injection of MLA (4 mg/kg, s.c.) or saline controls. Immediately following reinstatement, mice were perfused for immunohistochemistry, to detect c-Fos expression in 40 µm coronal brain slices.
In the last experiment (Fig. 5), naive mice were treated as on the CPP reinstatement day and brains horizontally sliced to clearly individualise CA1 location.



REFERENCES: [1] Luchicchi A et al (2014) Front Synaptic Neurosci 6:24; [2] Wright VL et al (2019) Addiction Biology 24:590-603