α7 nicotinic receptor antagonism selectively reduces reinstatement to morphine conditioned place preference

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– INTRODUCTION –

Nicotinic acetylcholine receptors (nAChRs) mediate addiction to nicotine but also, more recently, have been implicated in modulating reward-oriented associated behaviour (1,2). This is important for mechanistic understanding but also has clinical relevance. Here we explore the roles of the α7 nAChR in modulating aspects of opiate reward learning.

The aim of this study was to examine the effect of antagonism of α7 nAChRs and of endogenous acetylcholine on morphine reward using conditioned place preference.

– RESULTS –

Does α7 nAChRs antagonism affect CPP?

1) MLA pretreatment has no effect on the acquisition of morphine-CPP

• Mice received either saline or MLA 20 minutes prior to each morphine or saline dose (red arrow). Treatment of groups are the same until the hashed bars.

• After repeated doses of morphine, mice spent more time in the morphine-associated chamber; this was not affected by MLA pretreatment.

2) MLA pre-treatment has no effect on the reconsolidation of morphine-CPP

On day 15, animals received one further conditioning trial and immediately after received either MLA or saline (red arrow). Treatment groups the same until the hashed bars. After repeated doses of morphine, mice spent more time in the morphine-associated chamber; this was not affected by MLA pre-treatment.

3) MLA pre-treatment significantly reduces reinstatement to morphine-primed CPP

Mice underwent conditioning and extinction training. MLA or saline was given 20 mins prior to morphine-primed (5mg/kg) reinstatement (red arrow).

• No significant effect of treatment (F(1,16) = 0.31, p=0.583) but a significant effect of time (F(2,32) = 13.48, p<0.001).

• Post-hoc: significant difference in time spent in the drug-paired side during habituation and post-conditioning in both treatment groups (Control p=0.001, MLA p=0.105, n=27-28/treatment group).

• Significant difference between reinstatement in the two treatments (p=0.002, 27-28 treatment group).

• Therefore, α7 nAChRs may make a contribution to controlling reinstatement to morphine-CPP in C57BL/6J mice, and this supports and extends previous reports in mammalian models.

Does activating α7 nAChRs affect CPP?

1) PAM pre-treatment has no effect on the acquisition of morphine-CPP

Mice received either control or PAM 20 minutes prior to each morphine or saline dose (red arrow). Treatment of groups the same until the hashed bars. After repeated doses of morphine, mice spent more time in the morphine-associated chamber; this was not affected by PNU1 pre-treatment.

• Significant effect of treatment (F(1,16) = 6.62, p=0.022) but not treatment (F(1,16) = 0.31, p=0.583).

• Post-hoc: significant difference in time spent in the drug-paired side during habituation and post-conditioning in both treatment groups (Control p=0.001, MLA p=0.105, n=27-28/treatment group).

• Significant difference between reinstatement in the two treatments (p=0.002, 27-28 treatment group).

• Therefore, α7 nAChRs may make a contribution to controlling reinstatement to morphine-CPP in C57BL/6J mice, and this supports and extends previous reports in mammalian models.

– CONCLUSIONS –

• Morphine elicits a robust CPP response.

• The α7 nAChR antagonist, Methyllycaconitine (MLA) had no effect on the acquisition or reconsolidation of morphine-CPP.

• MLA significantly reduced morphine-primed reinstatement of CPP, implicating α7 nAChRs in the memory retrieval of morphine paired cues.

• PAM, a positive allosteric modulator had no effect on the acquisition of morphine CPP, suggesting that potentiating endogenous acetylcholine has no effect on forming morphine associated memories.

• This effect on reinstatement contrasts with the clear absence of an effect by MLA on acquisition and reconsolidation.

– REFERENCES –

1) To test the effect of α7 nAChR antagonist on CPP

Methyllycaconitine (MLA) an α7 selective nAChR antagonist (4mg/kg, i.p.) was given before morphine (10mg/kg, i.p) at the 3 stages of the CPP protocol (outlined below):

1) 2) To investigate the effect of α7 activation or potentiation on CPP

Mice received PNU 120596, a positive allosteric modulator, before morphine (10mg/kg, i.p) at acquisition.

– SUPPLEMENTARY DETAILS –

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