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Distinct role of kappa opioid receptor in attenuating relapse to morphine/methamphetamine (polydrug) dependence in mice

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SUMMARY

A Combination of 0.3mg/kg buprenorphine and 1.0 mg/kg naltrexone treatment shows a promising result due to its ability to attenuate reinstatement (relapse) in morphine/methamphetamine (polydrug)-dependent mice in a conditioned place preference (CPP) model. This prompted us to identify which opioid receptor that contributes to its anti-relapse activity. Using the same CPP model, 10 mg/kg nor-BNI (a selective kappa opioid receptor [KOR] antagonist) was used to evaluate the involvement of KOR in mediating relapse to polydrug dependence. By applying the immunohistochemistry (IHC) technique, the investigation was extended to the mice brain using KOR antibody (EPR18881), focusing on the brain regions that are abundant in KOR density. The results showed that nor-BNI alone failed to attenuate relapse to polydrug dependence. However, the IHC results proved that the number of KOR significantly increased in the striatum during reinstatement compared to post-conditioning ($p < 0.05$). The KOR was significantly suppressed in the treatment group which strengthens the findings from previous studies proving that the KOR plays an important role in mediating relapse to polydrug dependence.

INTRODUCTION

The kappa opioid receptor (KOR) has been associated with relapse to many drugs of abuse. Therefore, this receptor may be used as a potential target to prevent relapse to drug taking, which includes polydrugs (Wee 2012). This study aims to investigate the distinct role of KOR in mediating relapse to morphine/methamphetamine (polydrug dependence) at behavioral and brain level.

MATERIALS AND METHODS

All experiments were conducted using adult male Swiss albino mice weighing around 25 – 35 g (8 – 10 weeks old). The experimental protocols were approved by the IIUM's Institutional Animal Care and Use Committee (IACUC).

In a three-compartment CPP model, the mice were made dependent on 7.52 mg/kg morphine and 1.0

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mg/kg methamphetamine during the conditioning phase. After successful extinction, and prior to reinstatement, the mice received either the treatment (a combination of 0.3 mg/kg buprenorphine/1.0 mg/kg naltrexone), a selective KOR antagonist (10 mg/kg nor-BNI), or saline (control).

The brain tissues were harvested and processed after the behavioral experiment was completed. The rabbit monoclonal to KOR antibody (EPR18881) was used to identify the KOR at four different brain regions (amygdala, hippocampus, prefrontal cortex and striatum). All data were statistically analysed using a paired-samples t-test.

RESULTS AND DISCUSSION

Polydrug dependence was significantly seen to have developed in all three groups ($p < 0.001$) in comparison to their own baseline. A non-significant reinstatement to polydrug was observed with 19.29± 14.32% preference towards the drug-paired compartment (n=13) in the treatment group, where reinstatement was successfully attenuated in 6 mice that did not develop stereotyped behaviour. The non-significant polydrug reinstatement was proven not to be caused by KOR antagonism, since nor-BNI itself failed to attenuate reinstatement to polydrug dependence.

Further investigation done using IHC technique proved that the dose of naltrexone used successfully suppressed KOR expression in all brain regions studied. It was discovered that the number of KOR significantly increased in the striatum during the reinstatement (relapse) phase compared to post-conditioning (33.39 ± 5.60 and 16.73 ± 5.26 respectively, $p < 0.05$) and also markedly increased in the hippocampus (65.25 ± 4.13 and 51.11 ± 6.87 respectively) in the control (saline) group.

The hyperactivity of KOR system has been linked to dysphoria which leads to drug relapse (Gerra, 2006). The increase of KOR in the striatum and hippocampus suggests that polydrug withdrawal truly affects the KOR system. These two brain regions have a high density of KOR (Zhou 2015). Therefore, it is believed that the suppression of this receptor might prevent drug relapse, including to polydrugs which has been shown by the IHC results where the KOR expression was significantly suppressed in all the four brain regions.

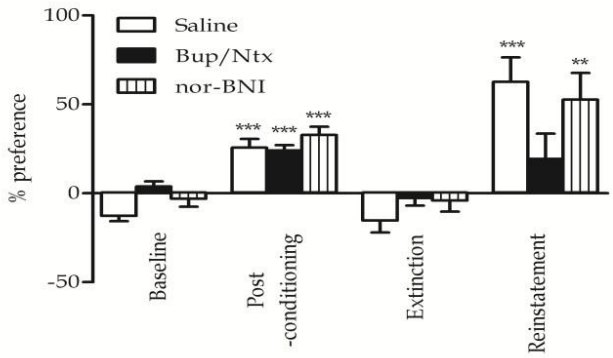

*Fig. 1. CPP test for morphine/methamphetamine-conditioned (polydrug) (saline [control]) (n = 11), buprenorphine/naltrexone [Bup/Ntx] [treatment] (n = 13) and nor-BNI groups (n = 10). ** indicates a very significant difference ($p < 0.01$) from baseline and *** indicates an extremely significant difference ($p < 0.001$) from baseline.*

CONCLUSIONS

Although there are conflicting evidence suggesting the activation of KOR system is the key to prevent relapse to drug taking, this study prove that number of KOR increase during reinstatement. The mice that response well to buprenorphine/naltrexone treatment has no expression of KOR, suggest that KOR system can be manipulated to treat polydrug dependence.

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