Selective modulation of the infralimbic cortex activity regulates reinstatement of cocaine-context associations in mice

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Abstract

Mechanisms underlying relapse into cocaine are not yet fully understood. Animal studies suggest a pivotal involvement of the infralimbic (IL) division of the medial prefrontal cortex, but causal evidence is lacking. Here, we employed chemogenetics to selectively modulate the IL during reinstatement of cocaine-related behaviours in the conditioned place preference (CPP) model. To this aim, C57BL/6J mice (*N* = 28) received intra-IL microinjections of adenoassociated viral vectors containing either silencing (AAV_5-CaMKIIα-hM4Di-mCherry) or stimulatory (AAV_5-CaMKIIα-hM3Dq-mCherry) designer receptors, or a control vector (AAV_5-CaMKIIα-mCherry). Animals were trained to acquire a CPP induced by increasing doses of cocaine (2-16 mg/kg) and later submitted to forced extinction. Four weeks after AAV infusion, mice received Clozapine N-oxide (5 mg/kg) 30 minutes before undergoing a cocaine-primed (7.5 mg/kg) CPP reinstatement test. Ninety minutes later animals were perfused, and brains dissected to analyse the expression of mCherry and c-Fos proteins in the IL. We found that CPP reinstatement was significantly increased after silencing IL compared to the control group, while blocked after selective stimulation of this brain region. In turn, immunofluorescence analyses revealed a ~0.5-fold decrease and a ~3-fold increase in mCherry /c-Fos co-labelling in AAV-hM4Di and AAV-hM3Dq groups (respectively) compared to the control group. Taken together, our data indicate that the IL is causally involved in the reinstatement of cocaine-related maladaptive behaviours and stands out as a target for modulation to prevent cocaine relapse.

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