PHARMACOGENETIC INHIBITION OF THE INFRALIMBIC CORTEX PROMOTES REINSTATEMENT OF COCAINE-CONTEXT MEMORIES IN MICE (C48)

Topic
AS08 Diseases of The Nervous System (including, infective and psychiatric)

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Abstract Body
Relapse is one of the main problems concerning treatment of cocaine use disorder. Lesion and pharmacological studies have suggested that the infralimbic cortex (IL), a division of the medial prefrontal cortex, is involved in extinction and reinstatement of associative memories, including those involving drug-context learning. However, more selective strategies are needed to elucidate the involvement of IL in the long-term maintenance of drug-related maladaptive behaviours. Here, we employed pharmacogenetics to assess the causal role of IL in the reinstatement of a cocaine-induced conditioned place preference (CPP). For this purpose, adult C57BL/6J mice received bilateral intra-IL microinjections of an adeno-associated viral (AAV) vector containing the hM4Di designed receptor (AAV_5-CaMKII-hM4Di-mCherry; AAV-hM4Di, n = 11) or a control vector (AAV_5-CaMKII-mCherry; AAV-control, n = 9) prior receiving training in the cocaine-induced CPP model. After habituation, animals received compartment-paired conditioning by increasing doses of cocaine (2-16 mg/kg/day, i.p.) and were tested for cocaine-CPP, after which they were subjected to forced CPP extinction and then re-tested for cocaine-CPP. On day 37 after AAV infusion, mice received Clozapine N-oxide (CNO, 5 mg/kg, i.p.) and 30 min later were tested for cocaine-primed (7.5 mg/kg, i.p.) CPP reinstatement. Ninety minutes after, animals were perfused, and brains dissected. Our results indicated that both groups acquired and subsequently extinguished cocaine-CPP. However, only the AAV-hM4Di group showed a significant preference for the cocaine-paired compartment during the CPP reinstatement test. Immunofluorescence analyses of c-Fos expression in IL revealed a decrease of ~60% in $mCherry^+/c\text{-}Fos^+$ co-labelling in the AAV-hM4Di group, suggesting reduced IL neural activity during CPP reinstatement. Therefore, our data suggests that the IL plays a causal role in relapse to cocaine-related maladaptive behaviours, highlighting its importance as a potential therapeutic target. Funding: PID2020-113806RB-I00, 08-2021-AREA3, B1-2020_06, FPU20/00908, PRE2018-085673, PREDOC_01094, POSTDOC_ 21_00222. II Plan Propio de Investigación, Transferencia y Divulgación Científica de la UMA.