

TITLE

Reduction of adult hippocampal neurogenesis modifies brain functional connectivity and enhances cocaine-seeking in mice

ABSTRACT

Recently, adult hippocampal neurogenesis has been proposed as a putative neuroplastic mechanism involved in those behavioural processes. In this work, we studied the effect of the inhibition of adult hippocampal neurogenesis using the DNA alkylating agent temozolomide (TMZ), in cocaine-induced conditioned place preference (CPP) behaviour. In a first experiment, we investigated both CPP acquisition/expression and the functional brain circuits underlying CPP expression in control and neurogenesis-reduced conditions by analysing c-Fos immunoreactivity (c-Fos IR) in hippocampal and extrahippocampal addiction-related areas. A second experiment was designed to study the involvement of adult-born neurons in the extinction and cocaine-induced reinstatement of drug-seeking in the CPP model. We performed two independent studies where adult hippocampal neurogenesis was inhibited either before or after the CPP was acquired. Our results showed that TMZ treatment had no effect on the acquisition of the cocaine-induced CPP, but c-Fos IR associated to the test trial (CPP expression) revealed an increased activity in some of the analysed brain areas in the CPP-TMZ mice. Correlational and multivariate analysis revealed that, under normal conditions, the hippocampus showed widespread functional connectivity with other brain areas and strongly contributed to the functional brain network associated with CPP expression. However, mice with reduced neurogenesis showed an alternative brain circuit. The results of the second experiment revealed that mice acquiring the cocaine-induced CPP under neurogenesis-reduced conditions were delayed in extinguishing their drug seeking behaviour. However, when neurogenesis was inhibited after CPP acquisition, extinction was not affected but an enhanced long-term CPP retention was found, suggesting that the role of the adult-born neurons may differ depending on whether they are generated before or after drug-contextual associations are established. Importantly, cocaine-induced reinstatement of CPP behaviour was increased in the TMZ mice, regardless of the time of neurogenesis inhibition. Funding: Spanish Ministry of Economy and Competitiveness (PSI2013-44901-P to L.J.S.; Subprograma RETICS Red de Trastornos Adictivos RD12/0028/0001, to F.R.F.). Author E.C-O. holds a 'Sara Borrell' research contract from the Spanish Carlos III Health Institute, Spanish Ministry of Economy and Competitiveness (grant number CD12/00455). Author D.L.G-M. holds a 'FPU' grant from the Spanish Ministry of Education, Culture and Sports (grant number FPU13/04819). Universidad de Málaga. Andalucía Tech, Campus de Excelencia Internacional.

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