Persistent drug-associated memories coexist with hippocampal-dependent cognitive decline and altered adult hippocampal neurogenesis in mice withdrawn from cocaine

M. Carmen Mañas-Padilla, Sara Gil-Rodríguez, Patricia Sampedro-Piquero, Fabiola Ávila-Gámiz, Fernando Rodríguez de Fonseca, Luis J. Santín, Estela Castilla-Ortega

Aims: Using a new animal model ('chronic' cocaine-induced conditioned place preference –CPP-paradigm), this work studied whether the long-term maintenance of cocaine-associated memories was concomitant to cognitive impairment and adult hippocampal neurogenesis (AHN) alterations. **Methods**: Male c57BL/6J mice were submitted to a CPP task treated either with cocaine (20 mg/kg/day) or saline for 14 days (n=10 per group). Bromodeoxyuridine (BrdU) was administered to label the new hippocampal neurons generated one week after the last cocaine dose. After 28 drug-free days, mice were assessed for the CPP memory and on a battery of emotional and cognitive behavioral tests. After completion of behavior, brains were collected for AHN analysis. **Results:** In mice treated with cocaine, preference for the cocaine-paired compartment (CPP memory) persisted over time. In addition, the cocaine-withdrawn mice overall displayed normal emotional behavior but they showed hippocampal-dependent cognitive impairment for novelty recognition (object and place) and spatial (reference and working) memory. The number of BrdU+ cells was unaffected, suggesting that cocaine withdrawal did not impair basal AHN. However, the cocaine-withdrawn mice excessively increased the number immature hippocampal neurons (doublecortin+) after behavioral training, in direct correlation with their cognitive performance, probably as a result of effortful learning. **Conclusions:** The CPP memory induced by cocaine remains unaltered after a prolonged period of abstinence, accompanied by defective acquisition of new learnings. Since the doublecortin+ neurons correlated with better cognitive performance in the cocaine-withdrawn mice, strategies that increase AHN could alleviate neurocognitive deficits induced by cocaine. Funding: PSI2015-73156-JIN; PSI2017-82604R; Plan Propio Universidad de Málaga