

ENHANCING ADULT HIPPOCAMPAL NEUROGENESIS WITH LYSOPHOSPHATIDIC ACID: A PROPOSAL FOR ERASING COCAINE CONTEXTUAL MEMORY

David Ladrón de Guevara-Miranda¹, Román Darío Moreno-Fernández¹, Sara Gil-Rodríguez¹, Cristina Rosell-Valle^{1,2}, Guillermo Estivill-Torrús³, Antonia Serrano⁴, Francisco J. Pavón⁴, Fernando Rodríguez de Fonseca⁴, Luis J. Santín¹, Estela Castilla-Ortega⁴

¹Departamento de Psicobiología y Metodología de las Ciencias del Comportamiento, Instituto de Investigación Biomédica de Málaga (IBIMA), Facultad de Psicología, Universidad de Málaga, Spain.

²Unidad de Producción de Reprogramación Celular, GMP-Iniciativa Andaluza en Terapia Avanzadas, Junta de Andalucía, Spain.

³Unidad de Gestión Clínica de Neurociencias, IBIMA, Hospital Regional Universitario de Málaga, Spain.

⁴Unidad de Gestión Clínica de Salud Mental, IBIMA, Hospital Regional Universitario de Málaga, Spain.

Aims. Stimulating adult hippocampal neurogenesis (AHN) has been uncovered as a promising approach in the manipulation of retrograde memories. This work aims to study whether increasing AHN with lysophosphatidic acid (LPA, an endogenous lysophospholipid with proneurogenic actions) promotes the forgetting of previously established cocaine-contextual associations.

Methods. C57BL/6J mice previously trained in a cocaine-induced conditioned place preference (CPP) paradigm were submitted to 23 days of withdrawal, during which they received repeated intracerebroventricular infusions of LPA, ki16425 (a selective LPA_{1/3} receptors antagonist), or vehicle solution. Then, CPP maintenance was assessed, and the causal role of AHN in this process was evaluated using a mediation analysis. In a complementary experiment, wild-type and LPA₁-null mice were acutely infused with LPA or ki16425 to determine the involvement of the LPA₁ receptor in the *in vivo* proneurogenic actions of LPA.

Results. The chronic LPA treatment significantly weakened the long-term retention of a previously acquired cocaine-CPP memory, an effect clearly mediated by a LPA-induced increase in the number of adult-born dentate granule cells. In contrast, the ki16425-treated mice displayed aberrant responses of initially decreased CPP retention that progressively increased CPP across the extinction sessions, in absence of effects on AHN. The histological studies suggested that the proneurogenic actions of LPA were related to the enhancement of cell proliferation and critically depended on the LPA₁ receptor function.

Conclusions. Our results suggest that the LPA/LPA₁-pathway acts as a potent *in vivo* modulator of AHN, and highlight the usefulness of a post-learning increase of adult-born hippocampal neurons as a strategy to promote the forgetting of cocaine-context associations. Enhancing AHN may lead to the renewal of the hippocampal circuitry, which might clear memories of previous cocaine experiences and, at the same time, facilitate the learning of new information, thus ameliorating the defective cognition frequently displayed by cocaine addicts.

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