More adult-born dentate gyrus neurons to weaken cocaine-related retrograde memories: an *in vivo* strategy employing exogenous lysophosphatidic acid.

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The post-training enhancement of adult hippocampal neurogenesis (AHN) has been receiving growing interest as a potential method to manipulate retrograde memories. Recent hypothesis suggest that the addition of adult-born dentate granule cells might promotes remodeling of pre-existing hippocampal circuits, which might both clear cocaine-related memories and facilitate the learning of new adaptive information. Here, we study the effect of stimulating AHN *in vivo* with exogenous lysophosphatidic acid (LPA, a biolipid with neurogenic properties) on the maintenance of retrograde cocaine-contextual associative memories. For this purpose, male C57BL/6J mice ($N = 28$) trained in a cocaine-induced Conditioned Place Preference (CPP) model were later submitted to repeated intracerebroventricular (i.c.v.) injections of LPA, Ki16425 (a selective LPA_1 receptor antagonist) or vehicle solution (bovine serum albumin, BSA) during withdrawal. Afterwards, the long-term persistence of the cocaine-CPP was assessed and the mediational role of AHN in this process was evaluated statistically. In an additional experiment, wild-type ($n = 14$) and mice lacking the LPA_1 receptor (maLPA$_1$-null; $n = 14$) received a single i.c.v. injection of LPA, Ki16425 or BSA in order to assess the implication of the LPA_1 receptor in the LPA-induced increase of AHN *in vivo*. Our results revealed that the chronic administration of exogenous LPA during withdrawal decreased the retention of a previously acquired cocaine-induced CPP. Furthermore, this effect was mediated by an LPA-induced increase in the number of adult-born dentate granule cells. In contrast, mice repeatedly treated with Ki16425 showed reduced cocaine-CPP retention, but they abnormally increased their preference for the cocaine-paired compartment throughout CPP extinction. Besides, no effects of Ki16425 on AHN were found. Immunohistochemical studies suggested that LPA stimulated cell proliferation and promoted neuronal maturation with a key role of the LPA_1 receptor. Taken together, these findings emphasize the relevance of LPA and its LPA_1 receptor as an *in vivo* modulator of AHN and the utility of the post-training increase of adult-born hippocampal neurons to weaken cocaine-context associations. This strategy could contribute to addiction therapy by promoting the maintenance of abstinence from cocaine and improve therapeutic success.

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