

Context-Associated Emotional Arousal Shapes Endocannabinoid Modulation of Spatial Memory Retrieval in Rats

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Compelling evidence indicates that cannabinoid drugs often induce biphasic effects on cognitive and emotional behavior depending on the aversiveness of the environmental context and the level of emotional arousal (Haller et al., 2009; Campolongo et al., 2012; Campolongo et al., 2013). It has been shown that variation in environmental aversiveness differentially influences spatial memory retrieval in rats (Akirav et al., 2004; Salehi et al., 2010) and that glucocorticoids interact with the endocannabinoid system in impairing contextual aversive memory retrieval (Atsak et al., 2012). Based on these findings we investigated the role of the hippocampal endocannabinoid system on spatial memory retrieval in rats under two experimental conditions that differed with respect to their training-associated arousal level. To this aim male adult Sprague-Dawley rats were trained in a Morris Water Maze task at two different water temperatures (19° C and 25° C), thus eliciting different levels of emotional arousal. Sixty minutes before the retrieval trial the cannabinoid agonist WIN55,212-2 was bilaterally infused into the hippocampus. We found that WIN55,212-2 impaired memory retrieval only in rats trained under the high arousing condition (19° C). In a second set of experiments, by employing the same experimental protocol, we examined if the endogenous cannabinoids anandamide and/or 2-arachidonoylglycerol could modulate spatial memory retrieval as well. To this aim the anandamide hydrolysis inhibitor URB597 or the 2-arachidonoylglycerol hydrolysis inhibitor JZL184 were infused bilaterally into the hippocampus 60 min before the retrieval trial. We found that URB597 did not alter spatial memory retrieval performances in any of the two experimental conditions. Interestingly, highly comparable with WIN55,212-2 effects, JZL184 impaired spatial memory retrieval only in rats trained at the lower, high-arousing, temperature. The present findings indicate that the hippocampal endocannabinoid system plays a key role in mediating emotional arousal effects on spatial memory retrieval, shedding light on the neurobiological mechanism involved in the differential impact of stress on memory processes.

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Atsak et al. (2012) *Proc Natl Acad Sci U S A.* 109, 3504-9.

Campolongo et al. (2012) *Front Behav Neurosci* 6, 11.

Campolongo et al. (2013) *Neuropsychopharmacology.* 38, 1276-86.

Haller et al. (2009) *Psychopharmacology (Berl)* 204, 607-16.

Salehi et al. (2010) *Learn. Mem.* 17, 522-30.