ROLE OF THE BASOLATERAL AMYGDALA IN THE HIPPOCAMPAL ENDOCANNABINOID MODULATION OF FEAR MEMORY RETRIEVAL IN RATS

Alessia Santori[1], Patrizia Ratano[1], Krista L. Wahlstrom[2], Ryan T. La Lumiere[2], Patrizia Campolongo[1]
[1]Department of Physiology and Pharmacology, Sapienza University of Rome, Rome - Italy, [2]Department of Psychological and Brain Sciences, University of Iowa, Iowa City - USA

The endocannabinoid system is crucially involved in the regulation of memory function and emotional responses. Cannabinoid receptors are highly expressed in cortico-limbic regions, where they modulate both excitatory and inhibitory signaling within specific neuronal circuits implicated in learning and memory processes for emotionally arousing experiences. Despite the engagement of the endocannabinoid neurotransmission in the modulation of memory acquisition and consolidation is well documented, its role in the retrieval of traumatic memories is still limited. Recent evidence has indicated that endocannabinoids are crucial modulators of the stress response, interfere with excessive retrieval and facilitate extinction, but still it remains uncertain how fluctuations in endocannabinoid content and activity in the hippocampal CA1area and basolateral amygdala (BLA) can influence the modulation of fear memory processes. Dysfunctional information processing is a common feature of stress-related disorders, such as post-traumatic stress disorder (PTSD), which is characterize by abnormal retrieval and insufficient extinction of traumatic memories. Of note, in PTSD hippocampal-dependent memory is compromised while amygdala-dependent memory is abnormally strengthened. Therefore, the goal of this study was to evaluate whether the endocannabinoid anandamide (AEA) and 2-arachidonoylglycerol (2-AG), in the CA1region of the dorsal hippocampus, differentially regulate fear memory retrieval depending on the environment-associated emotional arousal.
To this aim, male adult Sprague-Dawley rats were divided in different cohorts and tested for fear memory retrieval in a Contextual Fear Conditioning (CFC) task. We evaluated the effects of intra-CA1administration of the AEA hydrolysis inhibitor URB597or the 2-AG hydrolysis inhibitor KML29on freezing behavior. Rats were given bilateral intra-CA1administration of URB597(3, 10 or 30 ng/0.5μl), KML29(0.2, 2or 20 ng/0.5μl) or their vehicle 60 min prior to the CFC test. Animals were, then, sacrificed for brain dissection and histological analysis to assure proper cannula placement. Our findings indicated that enhancing endogenous levels of AEA into the dorsal CA1field of hippocampus did not affect the retrieval of contextual fear memory. However, when potentiated in the same brain region, the 2-AG signaling impaired contextual fear memory retrieval.
To investigate whether the BLA plays a role in the regulation of such hippocampal 2-AG effect, one group of rats was given temporal lesions of the BLA by bilateral infusion of the $GABA_A$ receptor agonist muscimol 2-hr prior to the CFC test. We found that hippocampal 2-AG modulation of memory retrieval required intact BLA. Indeed, the decrease of contextual fear memory retrieval induced by the inhibition of 2-AG hydrolysis in the CA1was abolished by BLA temporal inactivation.
To further characterize the BLA role in the hippocampal 2-AG modulation of memory retrieval, another group of rats was subjected to bilateral and intermittent optogenetic BLA inhibition during retrieval. In accordance with the pharmacological lesion results, we found that optogenetic BLA inhibition reverted the impairment of contextual fear memory retrieval induced by increased endogenous levels of 2-AG.
These data strongly suggest that bidirectional inputs between the CA1and the BLA are critical for enabling 2-AG hippocampal effects on fear memory retrieval.