Enhancing endogenous cannabinoid anandamide signaling in the basolateral amygdala impairs retrieval of aversive events in rats by activating the cannabinoid receptor sub-type 1

P. Ratano[1],S. Frusciante[1], P. Campolongo[1]

[1]Dept. Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy

The endocannabinoid system components (e.g. CB1 and CB2 receptors, Fatty Acid Amide Hydrolyse (FAAH) and Monoacylglycerol lipase (MAGL) enzymes, endocannabinoids) are widely expressed in brain areas, such as the hippocampus and basolateral complex of the amygdala (BLA), involved in regulating learning and memory processes. Although extensive data demonstrate the crucial role of the endocannabinoid system in the modulation of memory acquisition and consolidation, only limited evidence is available regarding its role on memory retrieval processes.
Therefore, here we investigated the effects induced by pharmacological manipulation of the endocannabinoid signalling in the dorsal hippocampus or the BLA on memory retrieval of aversive experiences. To this aim, adult male Sprague Dawley rats were trained in an Auditory Fear Conditioning task (AFC), and bilaterally infused into the dorsal hippocampus or the BLA with the FAAH inhibitor, URB597, or the MAGL inhibitor, KML29, in order to stimulate an endogenous increase of the endocannabinoids anandamide (AEA) and 2-arachinoyglycerol (2-AG), respectively.
In a first experiment, URB597 (3, 10, 30 ng/0.5 µl) or KML29 (2, 20, 200 ng/0.5 µl), were infused into the hippocampus 60 minutes before memory retrieval. We found that increasing AEA or 2-AG signaling in the hippocampus did not influence the retrieval of aversive memories. Conversely, when the FAAH inhibitor URB597 was infused in the BLA, at the dose of 10 ng, we found an impairing effect on retrieval of aversive memory, whereas the intra-BLA administration of KML29 did not induce any effect. In order to investigate whether the impairing URB597 effects on memory retrieval were dependent on CB1 receptor activation, we co-infused URB597 (10 ng) together with the CB1 receptor antagonist AM251 at a dose which does not alter bevahioral response per se (0.14 ng). AM251 administration blocked the impairing effect on memory retrieval induced by URB597, thus demonstrating that increased levels of AEA in BLA negatively modulate memory retrieval through a CB1 receptors-dependent mechanism.
Our results suggest that the endocannabinoid system is crucially involved in the regulation of memory retrieval process and might represent a new therapeutic target for treatment of neuropsychiatric disorders, such as post-traumatic stress disorder (PTSD), where a previous exposure to traumatic eventscould alter the response to trauma reminder and lead to mental illness.