Bidirectional regulation by the endocannabinoid in retrieval of fear memory using the fear conditioning task in mice

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Post-traumatic stress disorder (PTSD) is a psychiatric disorder associated with memories of traumatic experiences. In experimental animals, fear conditioning task is the most widely used as a model of PTSD. Previous studies have suggested a key role for the cannabinoid CB₁ receptors in the regulation of conditioned fear memory. Here, we investigated that the roles of endocannabinoid in fear memory on fear conditioning task, using the inhibitors of endocannabinoid hydrolysis. URB597, an anandamide hydrolysis inhibitor, significantly suppressed the expression rate of freezing behavior in both cue-elicited and contextual fear conditioning test in ICR mice. In contrast, JZL184, a 2-arachidonoylglycerol (2-AG) hydrolysis inhibitor, significantly increased the expression rate of freezing behavior. JZL195, a dual anandamide/2-AG hydrolysis inhibitor, also increased the expression rate of freezing behavior. Furthermore, we investigated the effect of URB597, JZL184 and JZL195 on anxiety-like behaviors with the elevated-plus maze test immediately after the fear conditioning tests. None of the above three inhibitors changed the time spent in open arms and the number of crossings. These findings suggest that the endocannabinoids play bidirectional roles in retrieval of fear memory. Namely, fear memory could be regulated by endocannabinoid, in particular, suppressively by anandamide but facilitatory by 2-AG.