Pharmacological modulation of fear expression by enhancers of the endocannabinoid tone depends on the neural subpopulation involved

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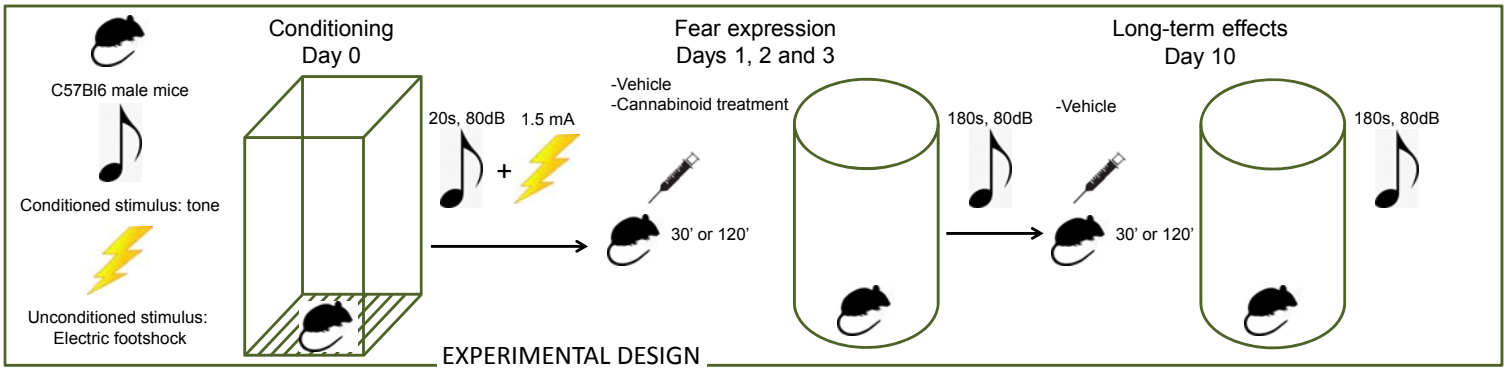
INTRODUCTION AND OBJECTIVE

Fear is an adaptive response that has evolved to provide protection from potential harm in the environment. Nevertheless, when fear is disproportionate to the situation, it can lead to the development of anxiety disorders [1]. Unfortunately, animal models of fear extinction do not allow testing pharmacological treatments chronically as fear response quickly declines during fear extinction. However, we have previously reported that continuous exposure to a conditioned stimulus induces a sustained fear response [2]. In the other hand, the endocannabinoid system (ECS) has been related to the extinction of fear, but not in acquisition or consolidation of aversive memories [3]. Noteworthy, aversive stimuli must exceed a certain threshold in order to activate the ECS and to decrease fear response [4], so ECS seems to act as a neuroprotector system against exaggerated fear responses.

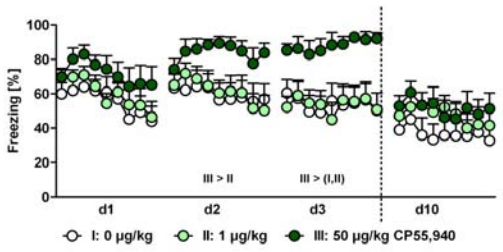
In the present study we have tested on an animal model of exaggerated fear diverse modulators of the ECS chronically to observe the implication of the ECS in fear extinction against a highly aversive stimulus.



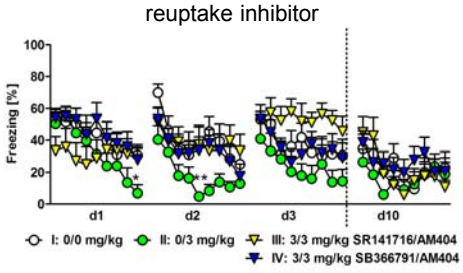
EXPERIMENTAL DESIGN

RESULTS

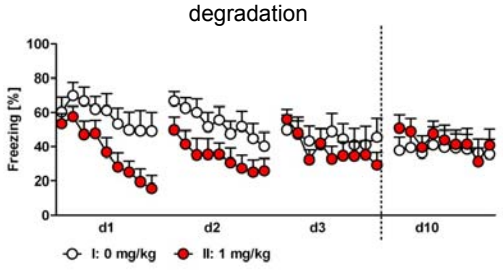
Treatment with CP55,940: CB1 receptor agonist



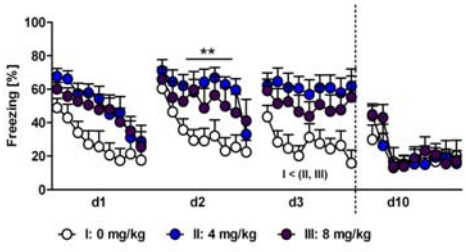
Treatment with AM404: Endocannabinoid reuptake inhibitor



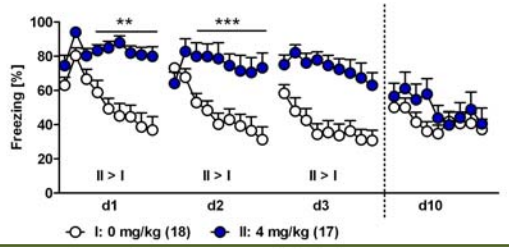
Treatment with URB597: Inhibitor of AEA degradation



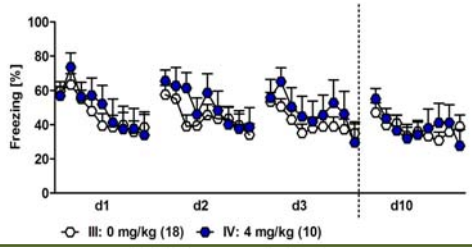
Treatment with JZL184: Inhibitor of 2-AG degradation



Treatment with JZL184 in GABA-CB1 WT animals



Treatment with JZL184 in GABA-CB1 KO animals



CB1 receptor exogenous agonist CP55,940 induced a significant increase of freezing response at the highest dose used (50 µg/kg). However, increase of endogenous cannabinoid levels (AEA and 2-AG) by AM404 caused the opposite effect, i.e. a decrease of the fear response. This decrease was dependent of the activation of TRPV1 and CB1 receptors since previous treatment with their antagonists (SB366791 and SR141716 respectively) counteracted this effect.

Increase of AEA levels (URB597 treatment) induced a significant decrease of freezing response similar to the AM404 treatment whereas increase of 2-AG levels (JZL184 treatment 4 and 8 mg/kg) caused the opposite effect alike to the CP55,940 treatment.

JZL184 induced an increase of freezing response in GABA-CB1 wild type animals, while this effect was totally abolished in their knock-out counterparts. This result shows that the activation, by 2-AG, of CB1 receptors in GABAergic terminals are responsible of the increased fear caused by the pharmacologic treatment with JZL184.

Data (mean ± SEM, sample sizes in brackets) were analyzed and depicted in 20s bins; x > y (e.g., III > I) – significant group differences ($p < 0.05$, ANOVA, followed by Newman-Keuls post-hoc test); * $p < 0.05$, ** $p < 0.01$ (significant group x time interval interaction, followed by Newman-Keuls test).

CONCLUSION

Our findings suggest that increased AEA levels might mediate acute fear relief via CB1 on glutamatergic neurons, while increased 2-AG levels promote the expression of conditioned fear via CB1 on GABAergic neurons. This dichotomy in endocannabinoid action has to be considered for the exploitation of the endocannabinoid system as a treatment of psychiatric disorders associated with exaggerated fear responses.

BIBLIOGRAPHY

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Authors report not having any conflict of interest