The administration of cannabidiol reduced reinforcement, motivation and relapse to alcohol

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1 EVALUATION OF PHYSIOLOGICAL EFFECTS OF ETHANOL

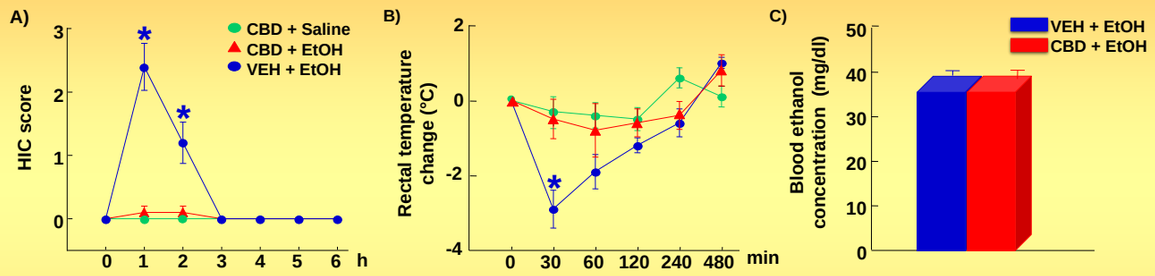

Figure 1. The dots represent the means and vertical lines ± the standard error of the mean (SEM) of: (A) the hourly measured HIC score after the administration of ethanol (4 g/kg p.o.); (B) results of ethanol (3 g/kg p.o.) induced hypothermia. Columns represent the means and vertical lines ± SEM of (C) blood ethanol concentration (BEC) (mg/dl) 1 h after the administration of ethanol (3 g/kg p.o.). *Represents values from CBD treated mice that are significantly different (Student's t-test, P<0.005).

2 VOLUNTARY ETHANOL CONSUMPTION (TWO BOTTLE CHOICE PARADIGM)

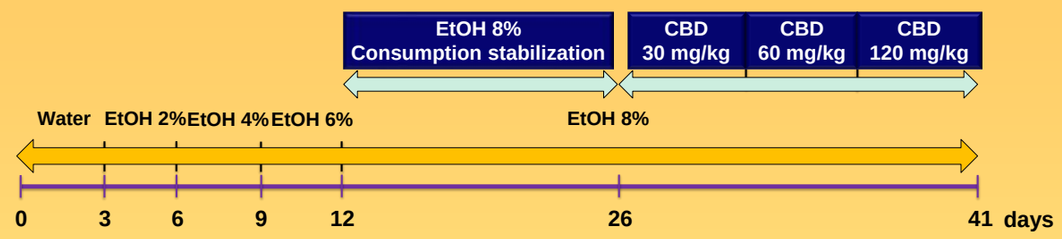

Figure 2. Schematic diagram of the two bottle choice paradigm. The ethanol concentration was gradually increased (2, 4, 6 and 8% v/v) every 3 days until ethanol 8% v/v was stabilized. After that, mice underwent treatment with CBD (starting dose was 30 mg/kg and it was increased every 5 days until reaching 120 mg/kg).

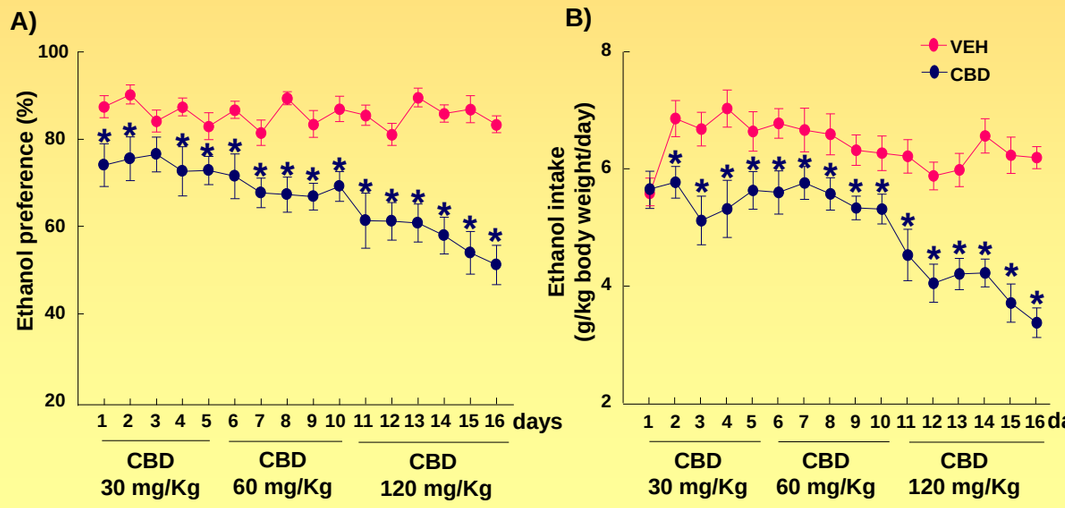

Figure 3. (A) Preference for ethanol consumption expressed as the ratio of the preference for ethanol consumption (ethanol preference = ethanol consumption/(ethanol consumption + water consumption)); (B) The measures were taken from volume of ethanol consumed every 24 hours and expressed as g/kg/day. The dots represent the means and vertical lines ± the standard error of the mean (SEM). *Represents values from CBD-treated mice that are significantly different (two-way RM ANOVA, P<0.005) (Student's t-test, P<0.005) from vehicle-treated group (VEH).

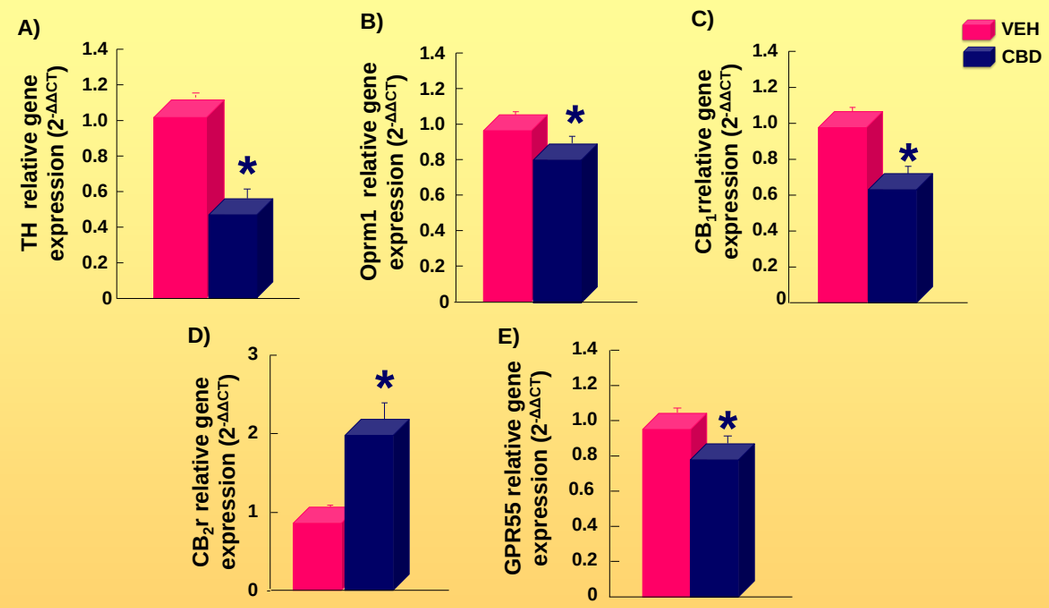

Figure 4. Real time PCR studies of tyrosine hydroxylase (TH) in the ventral tegmental area (VTA) and μ-opioid receptor (Oprm1), cannabinoid receptors (CB1r and CB2r) and G protein-coupled receptor 55 (GPR55) in the nucleus accumbens (NAcc) of C57BL/6J mice treated with increasing doses of CBD (30 mg/kg, 60 mg/kg and 120 mg/kg) during the two bottle choice paradigm. 2(-ΔΔCt) relative gene expression of: (A) TH, (B) Oprm1, (C) CB1 receptor, (D) CB2 receptor and (E) GPR55. Columns represent the means and vertical lines ± the standard error of the mean (SEM). *Represents values from CBD treated mice that are significantly different (Student's t-test, P<0.005) from vehicle-treated group (VEH).

SUMMARY AND CONCLUSIONS

The results of the present study revealed that:

1. The administration of CBD (60 mg/kg i.p) reduced hypothermia and handling-induced convulsions associated with high acute doses of ethanol. However, CBD did not modify blood ethanol concentrations.
2. CBD (30, 60 and 120 mg/kg, i.p.) significantly decreased ethanol consumption and preference in the two bottle choice paradigm.
3. A single s.c. administration of a microparticle formulation providing CBD continuous controlled release (30 mg/kg/day) significantly reduced ethanol intake and motivation to drink in the oral ethanol self-aministration paradigm (OEA).
4. The administration of CBD (60 and 120 mg/kg, i.p.) reduced alcohol induced relapse in the OEA.
5. These behavioral alterations were accompanied by gene expression alterations in cannabinoid (CB1r, CB2r) and GPR55 receptors, and Oprm1 in the NAcc and TH in the VTA.

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No potential conflict of interest

3 ORAL ETHANOL SELF-ADMINISTRATION

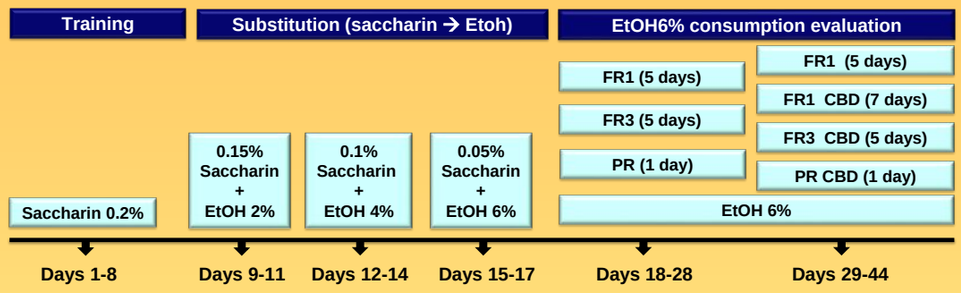

Figure 5. Schematic diagram including the different experimental phases of ethanol self-administration FR1=fixed ratio 1; FR3= fixed ratio 3; PR= progressive ratio.

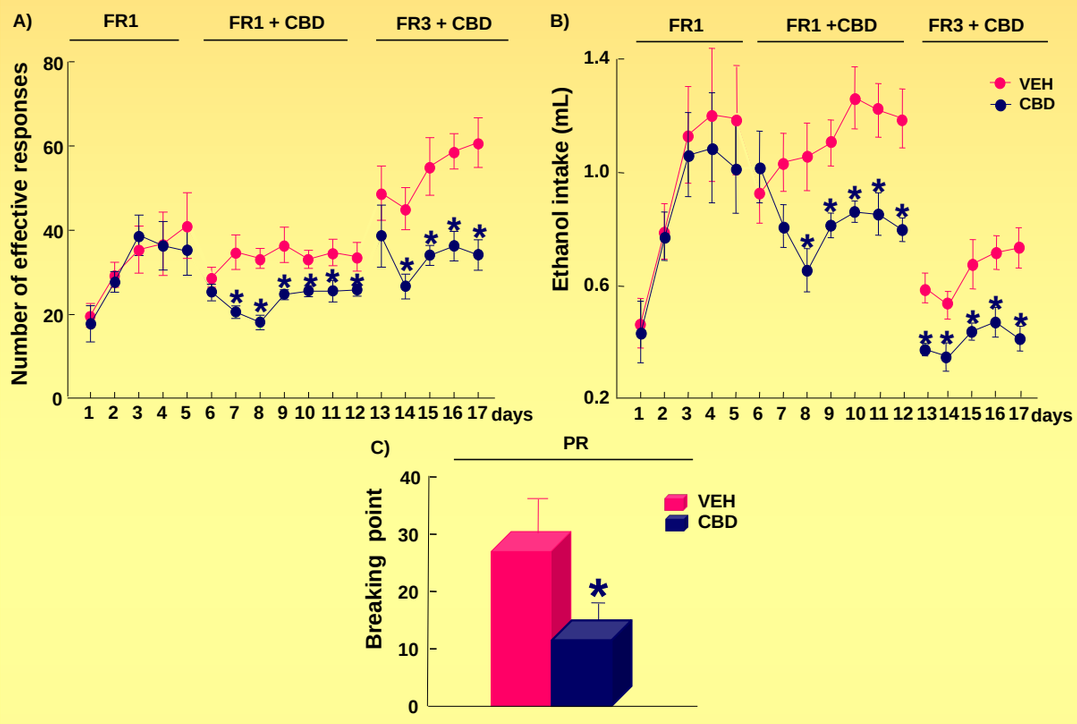

Figure 6. Number of effective responses (A) and ethanol intake (ml) (B) during the FR1 stabilization, FR1 + treatment and FR3 + treatment stages. (C) breaking point achieved during progressive ratio. The dots and columns represent the means and vertical lines ± the standard error of the mean (SEM). *Represents values from CBD-treated mice that are significantly different (panel A and B two-way RM ANOVA, P<0.005) (panel C, Student's t-test, P<0.005) from vehicle-treated group (VEH).

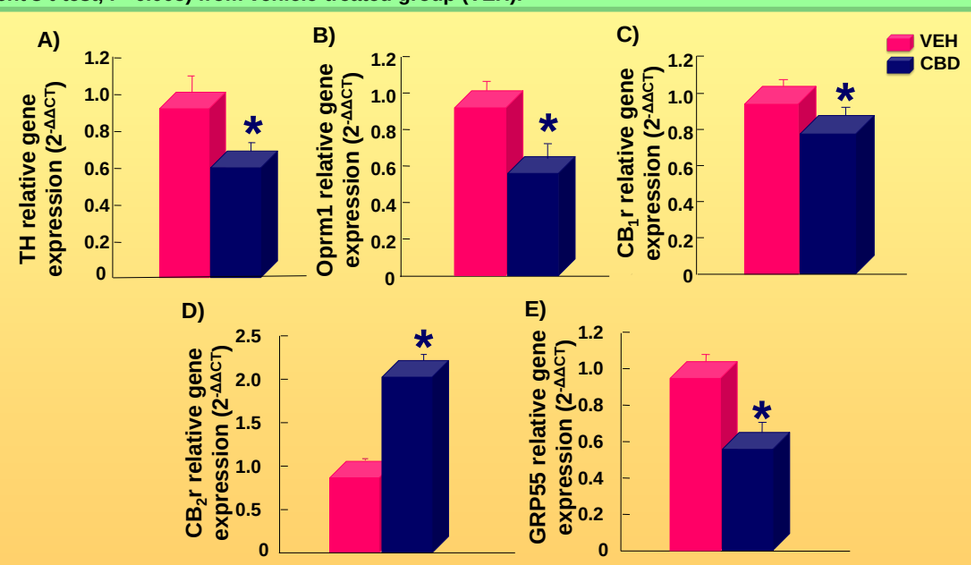

Figure 7. Real time PCR studies of Oprm1, GPR55, CB1r and CB2r in the NAcc and TH in the VTA of C57BL/6J mice treated with CBD (a single administration of a microparticle formulation providing CBD continuous controlled release (30 mg/kg/day, s.c.) during the oral ethanol self-administration. 2(-ΔΔCt) relative gene expression of: (A) TH, (B) Oprm1, (C) CB1 receptor, (D) CB2 receptor and (E) GPR55. Columns represent the means and vertical lines ± the standard error of the mean (SEM). *Represents values from CBD treated mice that are significantly different (Student's t-test, P<0.005) from vehicle treated group (VEH).

4 EFFECTS OF CANNABIDIOL ON ETHANOL-INDUCED RELAPSE

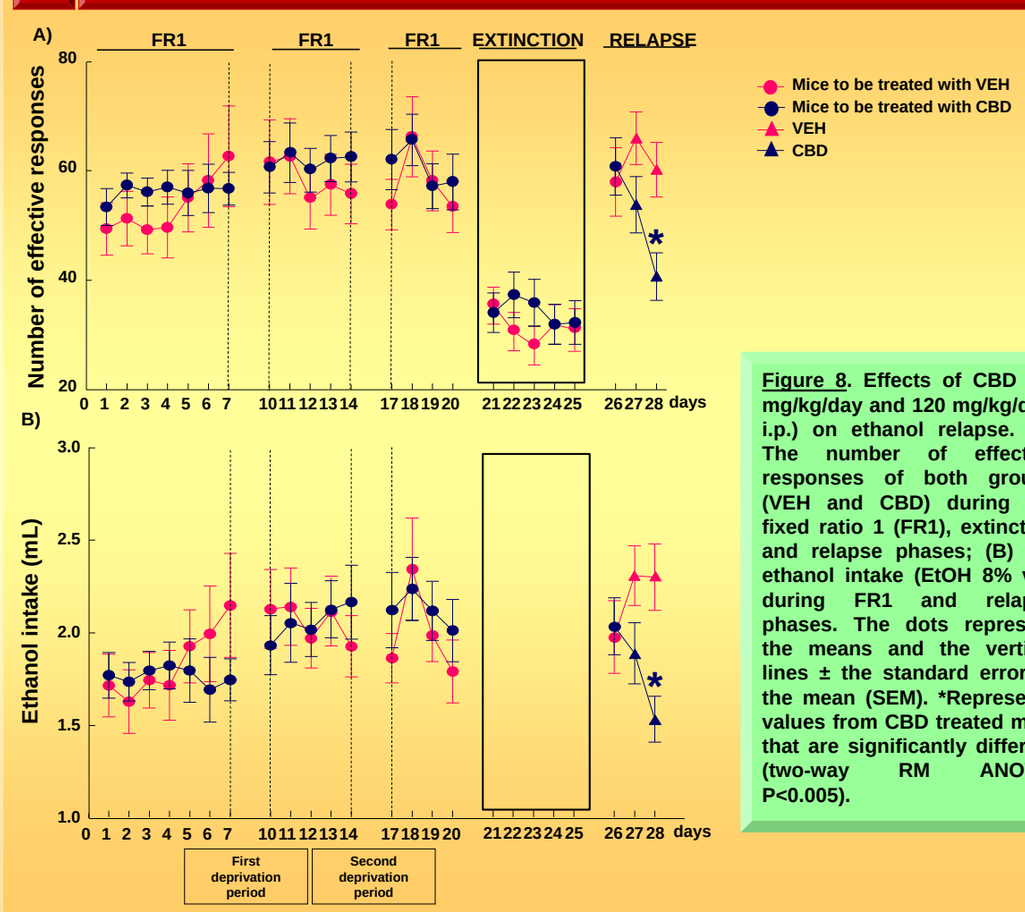

Figure 8. Effects of CBD (60 mg/kg/day and 120 mg/kg/day, i.p.) on ethanol relapse. (A) The number of effective responses of both groups (VEH and CBD) during the fixed ratio 1 (FR1), extinction and relapse phases; (B) the ethanol intake (EtOH 8% v/v) during FR1 and relapse phases. The dots represent the means and the vertical lines ± the standard error of the mean (SEM). *Represents values from CBD treated mice that are significantly different (two-way RM ANOVA, P<0.005).