Long term and delayed effects of ketamine and psilocybin in the preclinical chronic social defeat mouse model of depression

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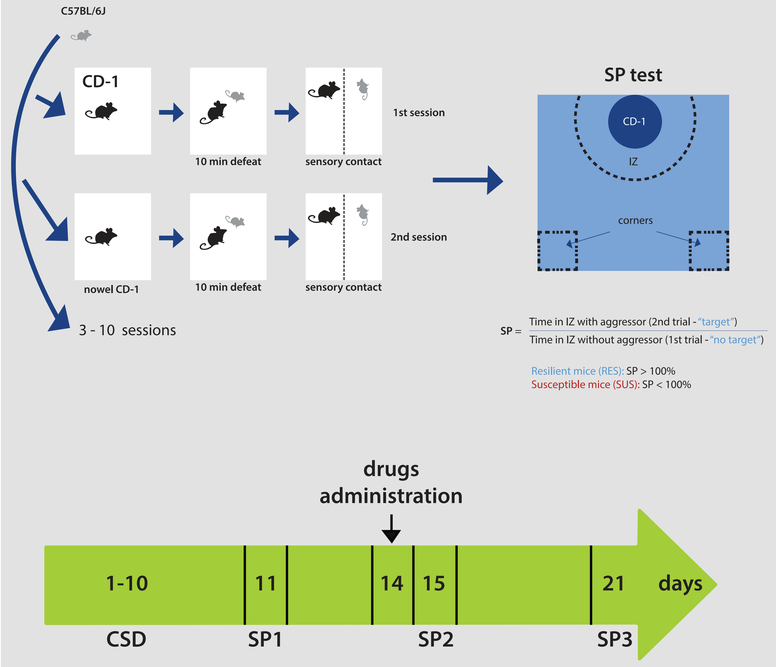
Introduction

Chronic social defeat (CSD) is a stress-induced psychosocial model of depression in mice that resemble depressive illness and additionally is selectively sensitive to clinically effective antidepressants. It is involving daily physical interaction and 24 hr sensory contact with an unfamiliar aggressive male. Following CSD, mice can be divided into stress-susceptible (SUS) or stress-resilient (RES) based on social avoidance behavior. Growing evidence suggests that non-competitive NMDA antagonist - ketamine as well as non-selective 5-HT2AR agonist - psilocybin and its derivatives exert antidepressant efficacy [1, 2].

In this study, we aim to determine social avoidance behavior in mice subjected to CSD and to assess the antidepressant effect of acute (24 hr) and long-lasting (7 days) ketamine (10 mg/kg, s.c.) and two doses of psilocybin (3 and 10 mg/kg, i.p.) after a single administration

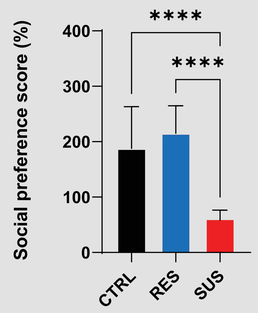
Methods

7 weeks old C57BL/6J male mice were subjected to 10 days of CSD procedure followed by the first social preference test (SP) to assess social avoidance phenotype distribution in mice when exposed to an "unfamiliar" CD-1 male mouse.



After that both SUS and RES groups were treated with either: vehicle (0.9% NaCl), ketamine (10 mg/kg) or psilocybin at two doses (3 mg/kg or 10 mg/kg). All animals were re-submitted to the second SP test 24 hr and again to the third one 7 days post-treatment.

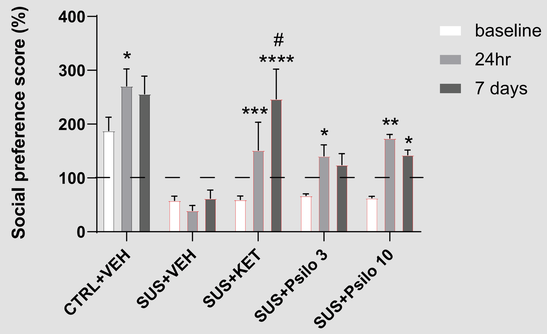
Phenotype distribution after CSD procedure



A SUS phenotype was identified in 51% of mice subjected to the procedure as indicated by a significant decrease in social preference score in comparison to RES and control animals (CTRL).

n= 9-32 per group. Mean ± SEM, ****p <0.0001. One-Way ANOVA followed by Fisher's LSD test.

Effect of ketamine and psilocybin on social avoidance phenotype in SUS mice

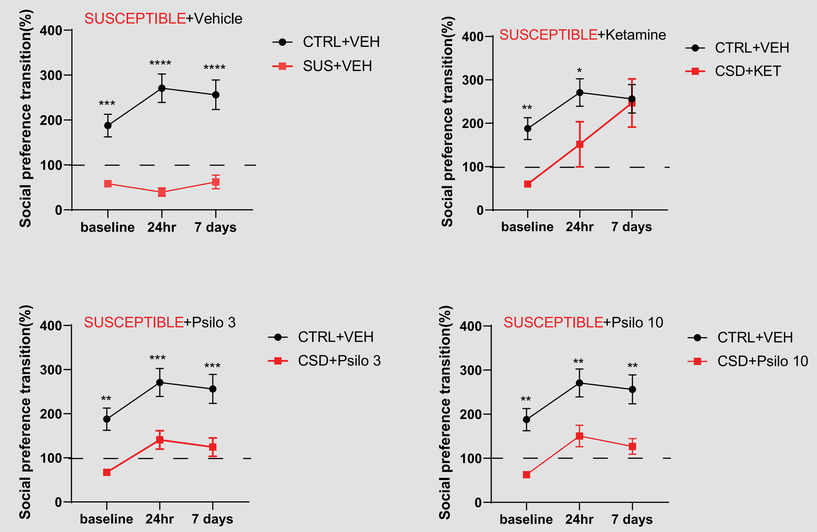


A single administration of ketamine (KET) resulted in a significant reduction of social avoidance in SUS mice both 24 hr and 7 days post-administration.

Psilocybin (Psilo) at a dose of 3 mg/kg significantly reduced social avoidance in SUS
animals but only 24 hr post-administration, whereas 10 mg/kg resulted in a significant reduction of social avoidance in SUS mice 24 hr as well as 7 days post-administration.

n= 5-14 per group. Mean ± SEM, *p <0.05, **p <0.005, ****p<0.0001 vs. baseline, #p<0.05 vs. 24hr. Mixed-effects ANOVA followed by Fisher's LSD test.

Social preference transition in SUS mice



Reversed SUS phenotype was shown after 24 hr and 7 days after a single administration of ketamine (KET) and psilocybin (Psilo). The SUS phenotype in the VEH-treated mice remained stable for 7 days.

n= 5-14 per group. Mean ± SEM, *p <0.05, **p <0.005, ***p<0.001 ****p<0.0001 vs. CTRL+VEH. Mixed-effects ANOVA followed by Fisher's LSD test.

Conclusions

Together, in this study we have shown that:

- The CSD procedure induced depressive-like behavior in a subset of mice which was reversed by a single dose of ketamine as well as both doses of psilocybin.
- The antidepressant effect of ketamine, as well as psilocybin, can persist over prolonged period after just a single administration.

References

1. Krystal JH, Sanacora G, Duman RS. Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. Biol Psychiatry. 2013; 73(12):1133-1141.

2. Carhart-Harris, R.L., Roseman, L., Bolstridge, M. et al. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. Sci Rep 7, 13187 (2017).

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