

Exploring the therapeutic potential of psilocybin in treatment-resistant depression: preclinical investigations in mice



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INTRODUCTION

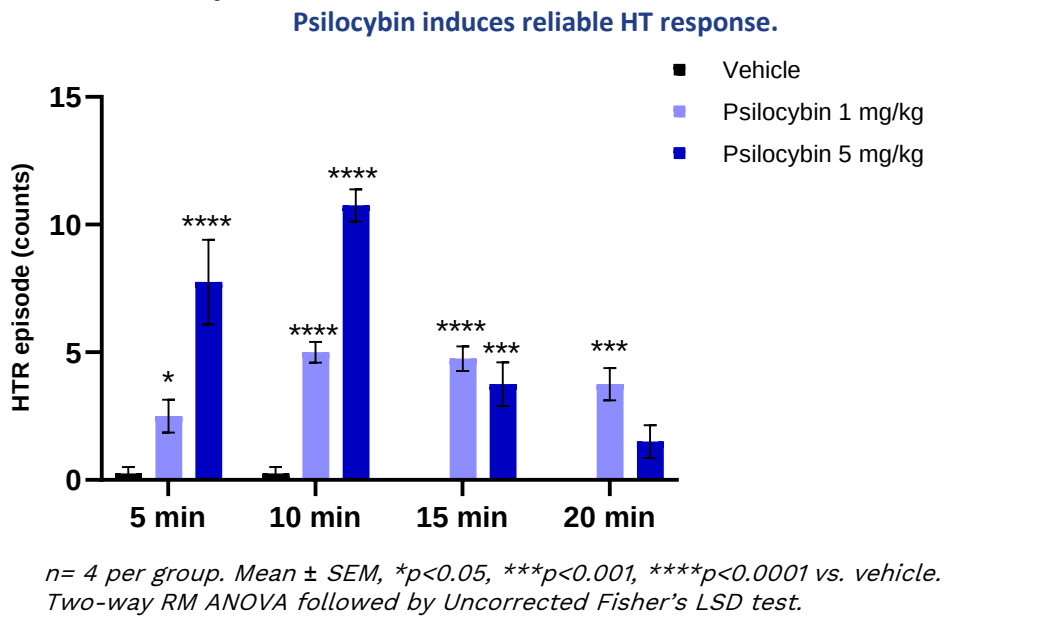
Treatment-resistant depression is a widespread global health concern, with urgent need for novel approaches. Recent research indicates that psilocybin and its derivatives hold promise as substances with potential therapeutic benefits. Psilocybin, a non-selective 5-HT_{2A}R agonist, has been found to alleviate depressive mood in individuals with treatment resistant depression (Carhart-Harris et al., 2017). Moreover, there is renewed interest in studying non-hallucinogenic LSD derivatives for their potential efficacy against depression. In this study we conducted various preclinical tests (commonly used in depression and anxiety research) to assess the effects of psilocybin on C57Bl/6 mice behaviour.

METHODS

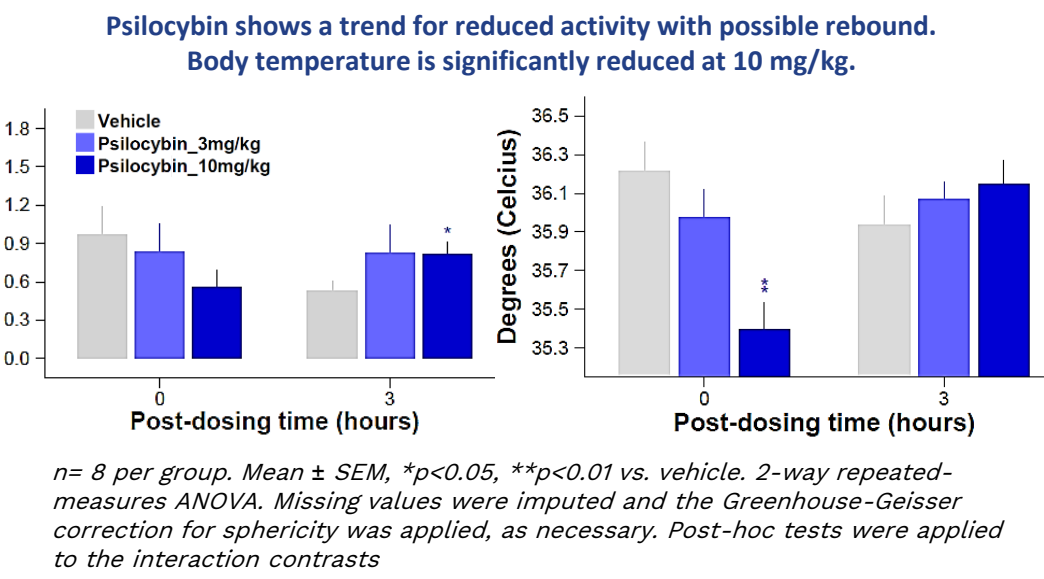
Psilocybin's hallucinogenic effect was assessed using Head Twitch Response (HTR) assay, measuring the number of rapid head shakes in mice immediately after treatment. Wireless electroencephalography (EEG) was used to monitor vigilance states and brain activity following psilocybin administration. Automatic sleep-wake scoring was performed, and the hourly distribution of wakefulness, NREM-sleep and REM-sleep was analyzed using proprietary Transpharmation software. The Forced Swim Test (FST) focused on immobility time of mice subjected to various psilocybin doses. Social Preference test (SP) was used to evaluate social avoidance behaviour in mice following a chronic social defeat procedure (CSD) and psilocybin treatment. Psilocybin was administered intraperitoneally (i.p.) at 1, 3, 5 and 10 mg/kg.

RESULTS

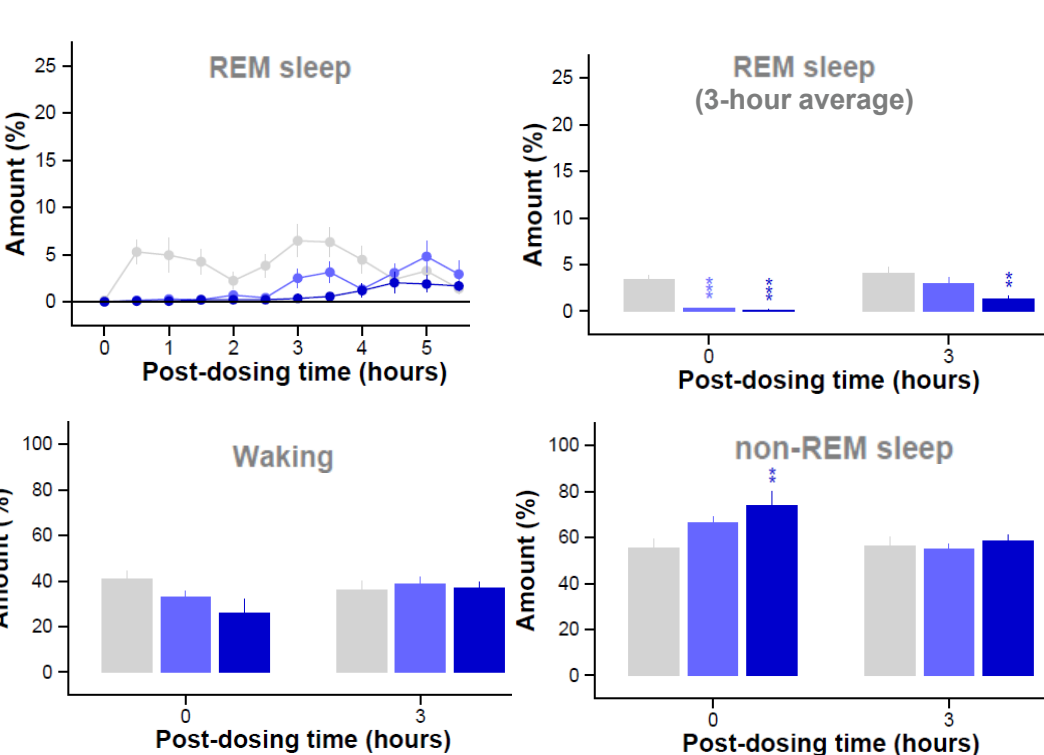
I. The Impact of Psilocybin on Head Twitch Counts in the HTR Assay



II. The Psilocybin Effect on EEG in Mice

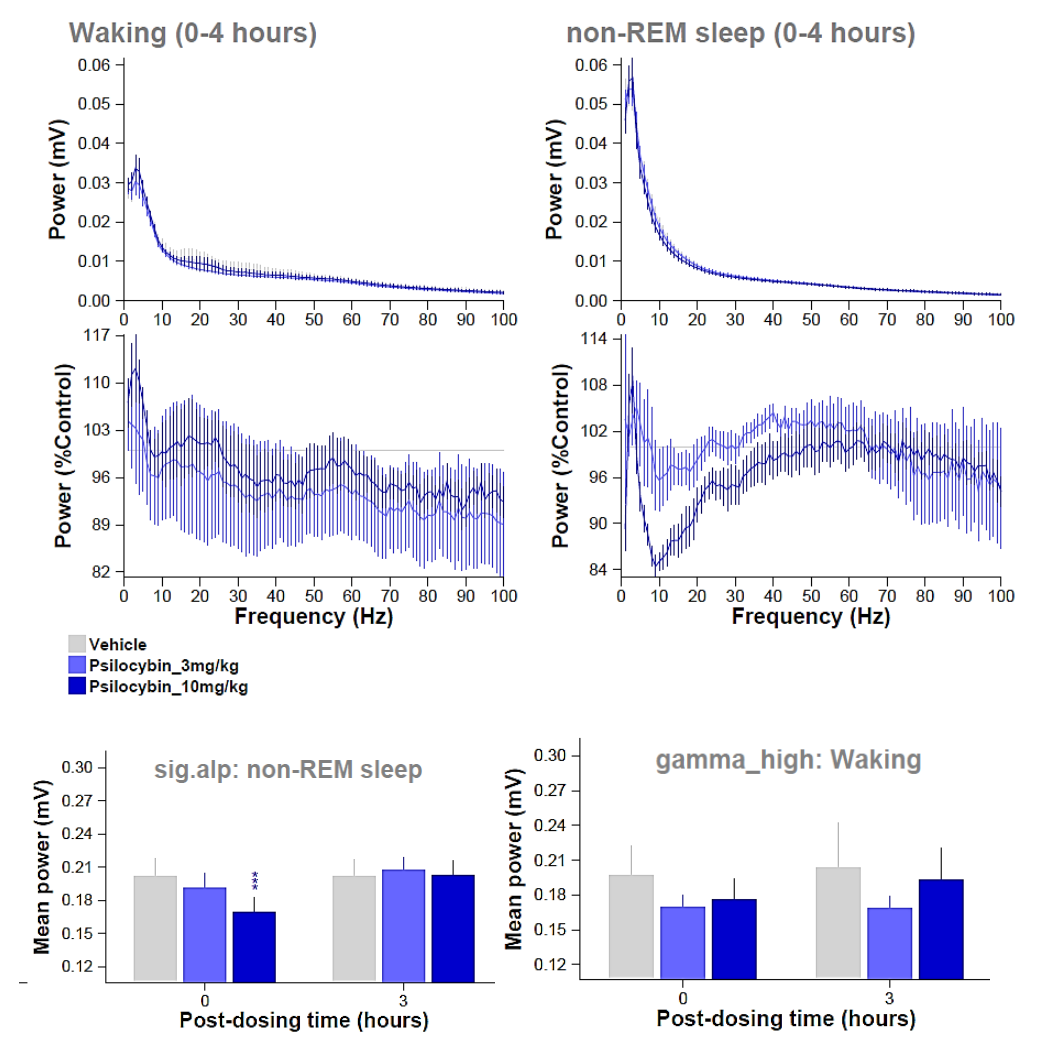


Psilocybin induces strong, long lasting and selective suppression of REM sleep



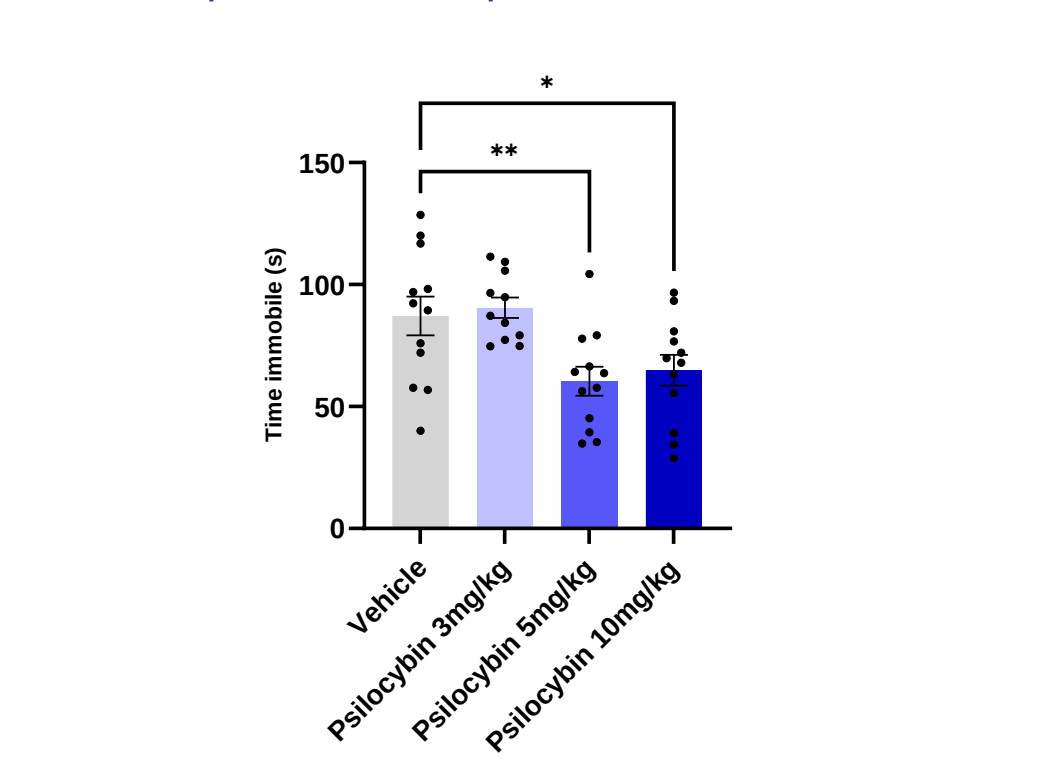
RESULTS

Psilocybin reduces sigma power in NREM & shows a trend for reduced waking high-gamma oscillations.



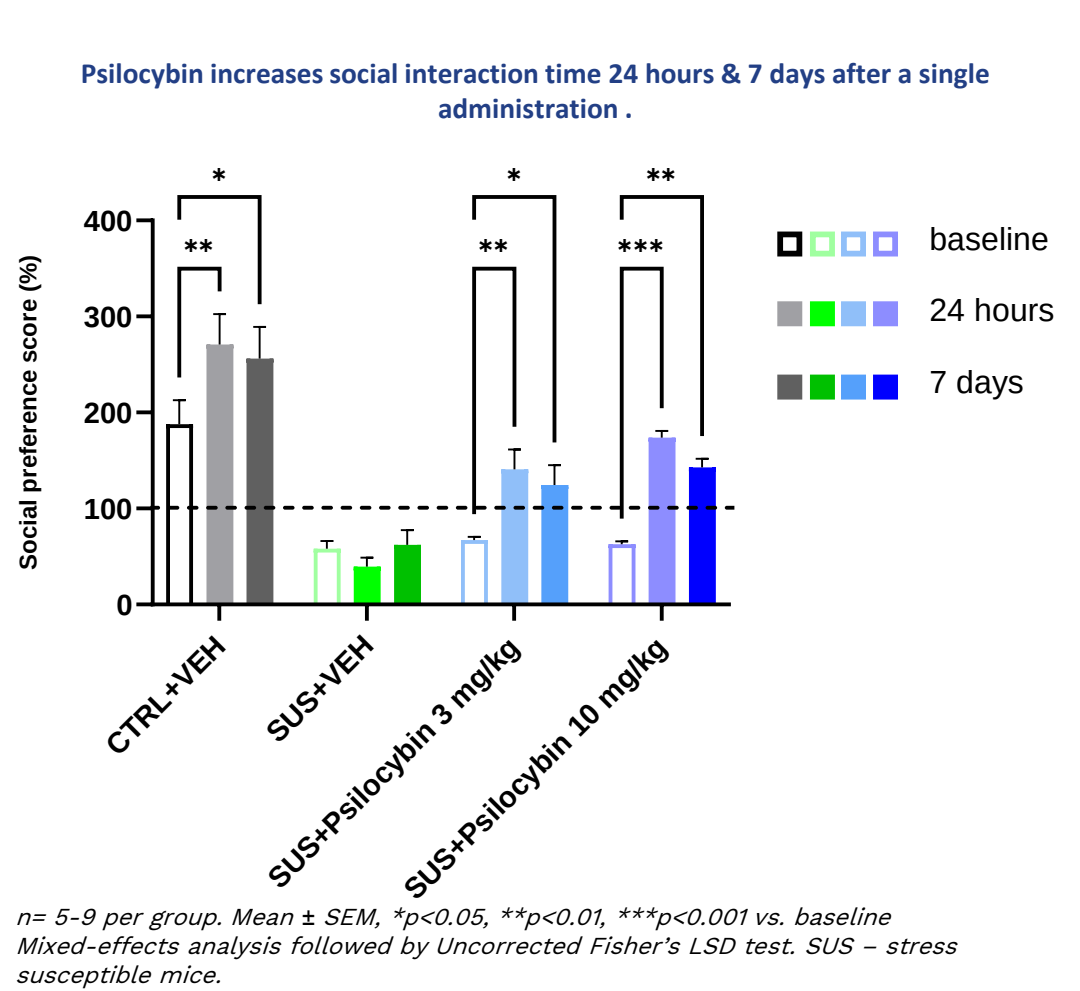
III. Acute Effect of Psilocybin (24 hr & 7 days) on immobility time in the forced swim test

Psilocybin reduces immobility time 24 hours after administration.



RESULTS

IV. Social Avoidance in Stress Susceptible Mice Pre-treatment (baseline) vs. Post-treatment (24hr & 7 days)



CONCLUSIONS

As expected, psilocybin evoked head twitches in C57Bl/6 mice, confirming 5-HT_{2A} receptor activation. Psilocybin briefly reduced wakefulness while increasing non-REM sleep but caused longer-lasting reductions in REM sleep for up to 4 hours. Psilocybin, particularly at 10mg/kg, produced a robust reduction in sigma-alpha oscillations during non-REM sleep. The two highest doses (5 & 10 mg/kg) presented antidepressant efficacy in the FST 24 hr post-administration. Psilocybin showed prolonged antidepressant efficacy (24 hr and 7 days) in CSD after a single administration. The studies described above have demonstrated the effectiveness of psilocybin in alleviating depressive symptoms.

REFERENCES

Carhart-Harris RL, Roseman L, Bolstridge M, Demetriou L, Pannekoek JN, Wall MB, Tanner M, Kaelen M, McGonigle J, Murphy K, Leech R, Curran HV, Nutt DJ. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. Sci Rep. 2017 Oct 13;7(1):13187. doi: 10.1038/s41598-017-13282-7. PMID: 29030624; PMCID: PMC5640601.