Psychoactive substances in the treatment of depressive disorder: Which screening test to choose?

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Introduction

More than half of depressed patients are resistant to standard treatments available on the market. Recent research has shown, that psychoactive substances, such as psilocybin, which is a nonselective 5-HT2A receptor agonist, present both short- and long-term therapeutic properties even after a single administration. Here we aim to determine which of the commonly used rapid pharmacodynamic response tests may be useful in assessing the antidepressant properties of the 5HT2A receptor agonists.

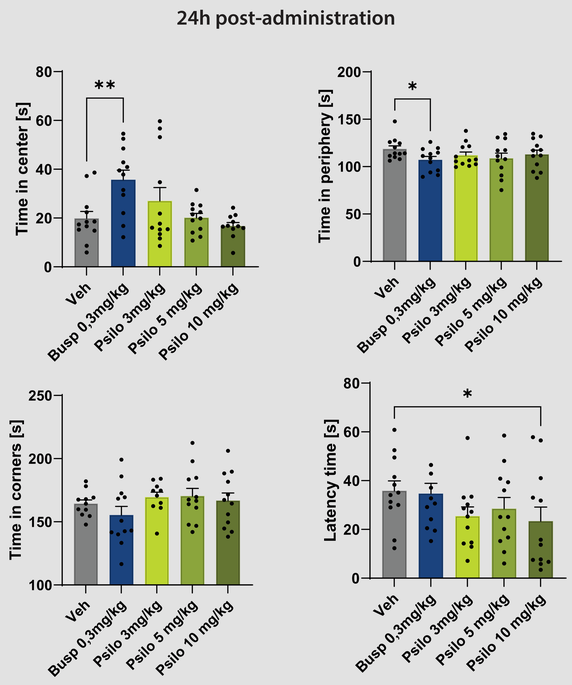
Methods

Young adult C57BL/6J male mice were subjected to 5 min open field (OF) test (580-600 lux, 40cm square arena) 24hr and 7d post administration of psilocybin or 30 min after buspirone administration (reference). After wash-out animals were administrated with either psilocybin or ketamine (reference). Forced swim test was performed 24hr and 7d post administration (6 min test, 58-60 lux). Another group of animals was subjected to 48h sucrose preference (SP) test 24hr post psilocybin administration (ketamine as reference group). After wash out and drug re-administration, tail suspension test (TST) (6 min test, 58-60 lux) was performed at 24hr and 7d timepoints.

All data were analyzed using the GraphPad Prism 9 statistical software. All data are presented as mean ± SEM. Outliers were removed from statistical analysis (outliers evaluated using ROUT method (Q = 5%).

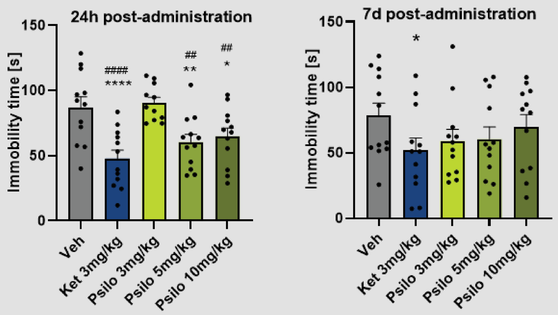
Results

In the **OF test**, only psilocybin at the highest dose (10mg/kg) showed anxiolytic effect 24h post-administration by decreasing the latency time to the first entry to the center area. None of the tested doses had a significant effect on time spent in the center, periphery or corners. Moreover, psilocybin at 5mg/kg is affecting locomotor activity 24h post-administration. For comparison, buspirone showed a clear anxiolytic effect, reduced time in the periphery and increased time in the center. We did not observe any anxiolytic efficacy of psilocybin 7 days post-administration.



*p<0,05; **p<0,005; Kruskal-Wallis with uncorrected Dunn's test.

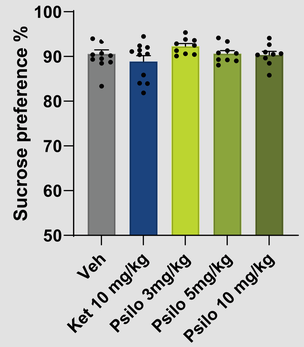
In the **FST test**, both ketamine and two highest doses of psilocybin (5 and 10 mg/kg;) presented antidepressant efficacy 24hr post-administration. Moreover, 7 days post-administration ketamine effect on immobility time was still visible.



*p <0.05, **p <0.005, ****p<0.0001 vs. **vehicle**, #p<0.05, ##p<0.05 vs. **PSILO 3.**
One-way ANOVA followed by Fisher's LSD test.

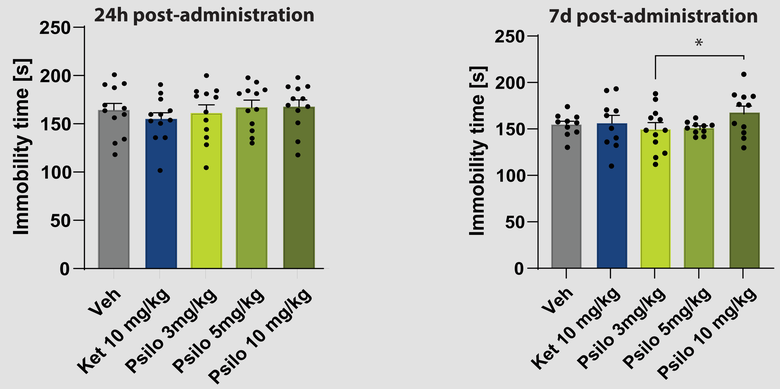
Results

In the **SP test**, vehicle-treated mice demonstrated high sucrose preference leaving us with no therapeutic window for potential drug effects.



One-way ANOVA followed by Fisher's LSD test.

Neither ketamine nor psilocybin (all doses) presented antidepressant efficacy in the **TST** at any of the timepoints.



*p <0.05; One-way ANOVA followed by Fisher's LSD test

Conclusions

- Not all the commonly used pharmacodynamic response tests are applicable to evaluate the antidepressant properties of the 5HT2A receptor agonists.
- Careful consideration is required for the selection of the appropriate testing platform.

References

1. Davis AK et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2021 May 1;78(5):481-489.

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